[COMMITTEE PRINT]

A REVIEW OF RISK ASSESSMENT METHODOLOGIES

REPORT

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LETTER OF SUBMITTAL

WASHINGTON, D.C., *July 6, 1982.*

Hon. DOUG WALGREN,
Subcommittee on Science, Research and Technology, Committee on Science and Technology, House of Representatives, Washington, D.C.

DEAR MR. CHAIRMAN: I am pleased to forward this CRS report on "A Review of Risk Assessment Methodologies," prepared for your committee.

Increasingly, policy-makers are considering scientific evidence and methods in formulating decisions on a host of products and processes that affect people's health and safety, including food additives, drugs, industrial processes, energy resources, transportation systems, and consumer goods. This report provides an overview of the scientific methodologies employed in risk assessments and discusses the appropriate uses and limitations of each. We trust that the report will prove to be a valuable resource for policymakers in understanding the bases for disagreements among technical experts on the nature or degree of some risks, and in utilizing the tools of risk assessment apporpriately in developing policies for a wide variety of risk agents.

The report was prepared by Dr. Gail H. Marcus, Assistant Chief of the Science Policy Research Division and Specialist in Science and Technology. It has been reviewed by Dr. Robert Civiak and Dr. Warren Donnelly of CRS, Dr. Michael Simpson, an AAAS Fellow with CRS, and several reviewers outside CRS.

Sincerely,

GILBERT GUDE, *Director.*

LETTER OF TRANSMITTAL

House of Representatives,
Committee on Science and Technology,
Washington, D.C., *March 15, 1983.*

Hon. Don Fuqua,
Chairman, Committee on Science and Technology
U.S. House of Representatives.

Dear Mr. Chairman: I transmit herewith a report entitled "A Review of Risk Assessment Methodologies" which has been prepared for the Subcommittee by the Congressional Research Service.

Over the last several years, the Subcommittee on Science, Research and Technology has conducted a number of oversight hearings, public forums, and legislative hearings on the use of risk analysis in the regulatory process. These activities have dealt with the use of risk analysis in such diverse fields as food additives, nuclear power, and air pollution. In these and other fields the techniques and methodology of risk assessment have much in common and this report provides a much needed and very helpful summary of these techniques and methodologies. We were fortunate in having Dr. Gail Marcus of the Science Policy Research Division at CRS develop this study for the Subcommittee.

I commend this report on risk assessment to your attention and to the attention of the members of the Committee on Science and Technology. I believe that it will be found useful by each member of the Committee as well as by many members of the House who have an interest in this matter.

Sincerely,

Doug Walgren,
Chairman, Subcommittee on Science,
Research and Technology.

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CHAPTER 1: INTRODUCTION

DEFINITION OF STUDY

Soon after primitive man first employed the simplest tool--perhaps it was a slingshot for downing his prey or a flint for starting his fire--he became a victim of risks of his own making. And ever since that time, he has been attempting to deal with those risks in one way or another. In recent years there has been an apparent heightening of concern about the risks our highly technological society imposes upon itself. Chemical wastes at Love canal, nuclear power plants, food additives such as saccharin and cyclamates, and a host of other risk issues have been splashed across the headlines. The debates on these issues, sometimes heated, have revealed many profound disagreements. Even the scientific bases of risk assessments are disputed.

Risk assessment is variously regarded; views range from those seeing it as "a formal extension of the almost automatic calculation of risks that everyone performs"[1] in their daily actions to those characterizing it as a hazard in its own right, as will be discussed later in the report.

This report examines the assessment techniques commonly used in the analysis of technology-based health and safety risks to human beings. Health and safety risks include any and all illnesses, injuries, mutagenic and teratogenic effects, or deaths resulting from a risk agent. Risks can be temporary or permanent, reversible or irreversible, minor or severe, short- or long-term, immediate or delayed.

The risk agents which can be included under the rubric of technology-based health and safety risk are many and varied. They include: substances used in growing, processing, and preserving our food; drugs and medical procedures; pollutants discharged into the environment (air and water) from our homes and our commercial and industrial enterprises; exposures to occupational hazards, industrial or mining accidents, and complex machinery; and miscellaneous exposures to possible illness, injury or death from the materials we use to build our homes and clothe our bodies, from the machinery we use for our comfort and convenience, from the products, like tobacco and alcohol, that we use for our pleasure, etc.

In effect, technological health and safety risks involve virtually the whole range of modern human activity, including the literally thousands of materials with which human beings come in contact, the hundreds of industries they operate, and a large variety of electrical and mechanical equipment they utilize. Table 1 lists the many classes of chemicals studied specifically for carcinogenisis alone, as reported in a series of monographs published by the International Agency for Research on Cancer (IARC). Still others of the many materials and industries that have been the subject of studies to quantify their risks, carcinogenic, mutagenic, and other, are indicated throughout this report.

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[1] Ramsay, William. On Assessing Risk, Resources, v. 68, Oct. 1981, p. 10-11.

TABLE 1. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN

Volume number (year)	Specific Title
Volume 1 (1972)	----------
Volume 2 (1973)	Some inorganic and organometallic compounds
Volume 3 (1973)	Certain polycyclic aromatic hydrocarbons and heterocyclic compounds.
Volume 4 (1974)	Some aromatic amines, Hydrazine and related substances, N-nitroso compounds and miscellaneous alkylating agents.
Volume 5 (1974)	Some organochlorine pesticides.
Volume 6 (1974)	Sex hormones.
Volume 7 (1974)	Some anti-thyroid and related substances, nitrofurans and industrial chemicals.
Volume 8 (1975)	Some aromatic azo compounds.
Volume 9 (1975)	Some aziridines, N-, S-; and O-mustards and selenium.
Volume 10 (1976)	Some naturally occuring substances.
Volume 11 (1976)	Cadmium, nickel, Some epoxides, miscellaneous industrial chemicals, and general considerations on volatile anesthetics.
Volume 12 (1976)	Some carbamates, thiocarbamates and carbazides.
Volume 13 (1977)	Some miscellaneous pharmaceutical substances.
Volume 14 (1977)	Asbestos.
Volume 15 (1977)	Some fumigants, the herbicides 2, 4-D and 2, 4, -5, -T, chlorinated dibenzodioxins and miscellaneous industrial chemicals.
Volume 16 (1978)	Some aromatic amines and related nitro compounds-hair dyes, colouring agents and miscellaneous industrial chemicals.
Volume 17 (1978)	Some N-nitroso compounds.

It should be noted that many substances which have been subjected to risk analyses are considered natural substances, in the sense that they occur naturally in food, drugs or other materials in common human use. Such substances include caffeine, salt, sugar, vitamins, natural drugs, etc. While these are not strictly the focus of major concern in the context of an examination of technological risks, they can, in a sense, be incorporated in this definition. Such risk agents can be examined by the same techniques as technological risks, and risk analysis can, in many cases, be employed to make similar types of individual and collective decisions regarding use of the risk agent.

Depending on the risk agent, there may be many steps of analysis required to quantify human risk for even one risk agent. The techniques necessary may include techniques to analyze single cell behavior, multi-cellular responses to risk, biological pathways through different organisms, physical distribution mechanisms in the air and water, and the performance of mechanical systems that might cause the release of a risk agent or might directly produce an injury.

Some of the many considerations that may be involved in a risk analysis are indicated in Table 2. This table is merely illustrative; it does not show all possibilities and does not indicate the specific sequence of steps that might be involved for any particular risk agent. Rather it indicates some of the possible steps that could be included in different cases; the necessity of any particular step in any particular case depends on the actual situation and the possible sequences of events in that situation. For example, one risk agent might be transmitted through air, to water, to the food chain, and then to man, while another is only transmitted through the air and then inhaled. Each would require the use of a different set of assessment techniques.

TABLE 2. GENERIC ELEMENTS OF RISK ASSESSMENT *

Element	Type	Examples	Assessment Techniques
Source of Risk:	Routine	Industrial emissions/food additives.	Field measurements.
	Nonroutine	Industrial/powerplant/transportation accidents.	Probabilistic analysis.
Pathways to Man:	Direct contact (external)	Industrial exposures	Field measurements.
	Air/water	Industrial effluents	Environmental models.
	Food chain	Mercury	Ecological models, biological models.
Impacts:	Injury/illness/death/genetic	Automobile accident/black lung disease/radiation exposure.	Epidemiological research, biological research, biological models.

* The presentation here is intended to be illustrative rather than comprehensive.

This report focuses primarily on an examination of the technical elements of risk analysis, and the uses and limitations of each major method used in risk assessment.[2] Many of these methods are basic to an understanding of risk, and a necessary element in making decisions regarding different risk management alternatives. Therefore, this report should provide useful background to anyone dealing with the subject of risk.

It should be noted that it is not the purpose of this study to examine in detail matters outside the scientific issues of risk assessment. Other important matters associated with risk are only briefly covered in this report. In particular, the area of risk management, incorporating all the technological and regulatory methods of reducing risk, as well as the social, economic, and ethical implications of different alternatives of reducing risk, are outside the direct purview of this study. Also, the issue of risk acceptability per se, that is, the issue of what levels of risk people will accept under different conditions, and the implications of this for risk management, are not explored in detail in this report. This report does incorporate some discussion of risk acceptability issues and risk management alternatives, primarily as they relate to specific risk assessment techniques, and provides reference to sources of additional information in these areas.

REASONS FOR IMPORTANCE

In addition to, or perhaps because of, subjective impressions from news reports of a world that seems increasingly fraught with danger, studies have shown a heightening of concern in recent years about the risks society imposes upon itself.[3] There are several reasons for this increased concern: the technological explosion, increasing scientific sophistication, improved health and safety, and growing consumer activism.

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[2] The need to apply many analytical steps is itself a potential limitation to a risk assessment, as it can compound errors and thereby reduce accuracy, reproducibility, and precision.

[3] See, for example, Risk in a Complex Society; A Marsh and McLennan Public Opinion Survey conducted by Louis Harris and Associates, Inc. New York, Marsh and McLennan, 1980. 66 p.

Because of the technological explosion of recent years, many people today come into daily contact with equipment and materials that simply did not exist a few years ago. Video displays in the workplace, a proliferation of appliances in the home, and new "miracle" drugs are only a sampling of the fruits of technology development. Therefore, there are many more potential hazards upon which to focus concern than there were even a few years ago.

Also, society as a whole has become far more sophisticated and far more educated about the consequences of some of the things it has done. Society has now had the experience of the early years of the industrial revolution, and has seen many products that once were regarded as panaceas develop into societal problems in their own right. Automobiles, for example, were once widely regarded as the perfect cure to the problem of pollution in the cities from the many horses then in use. Only later were the pollution hazards of automobiles even recognized.

Many of the diseases and other problems which were once the overwhelming human health concerns have, with the help of modern technology and scientific understanding, been largely eliminated--polio, smallpox, tuberculosis, cholera. Thus, fear and attention which would, in former times, have been directed towards those diseases may now be shifting to technological risks as the next frontier of human health hazards to be conquered. Also, because people are living longer, diseases which once remained latent now have time to develop.

In recent years, a combination of factors--educational level, leisure time, and media attention--has led to a growing consumer activism movement. Consumers increasingly are demanding a voice in all the decisions of government and industry that affect them--economic, environmental, health and safety. Decisions that might never have been questioned a generation ago are being closely and critically examined.

Because of all these factors, we are now attempting to prevent hazards before they happen. Through analytical and experimental techniques, we are examining technologies and materials far more carefully, and often in earlier stages of their development and use, than was formerly the case, and then publicly debating the findings and their implications for the use of that technology. Such intense scrutiny is making it more difficult, in many cases, to introduce new consumer products and use advanced industrial processes, and this entails real economic costs to society. Also, the equipment available for analyzing pollutants and contaminants has in many cases improved greatly. We can detect many environmental pollutants and food contaminants at far lower levels of concentration than we could before.[4] Therefore, we are finding some level of potential hazard in more and more things, often including substances that have been used and assumed safe for many years, such as formaldehyde, Tris, and many other materials. Often, we have not yet established whether a measurable danger exists at the lowest levels of chemical concentration we can measure. In a sense, our increasing knowledge is making it more and more difficult to make decisions regarding the use of many substances. Advances in research have even sometimes revealed that a solution used to reduce or eliminate one risk problem is, in fact, another risk problem in itself, such as was discovered after cyclamates were introduced as a safer substitute for saccharin.

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[4] House. Hearing before the Committee on Science and Technology, 97th Cong., 1st Sess., June 18, 1981. No. 41. Title: Societal Risks of Energy Systems. Testimony of Hon. Don Ritter, p. 13.

Ironically perhaps, in view of the increasing levels of concern and the restrictions these concerns are imposing on new developments, many of our activities have actually become safer than they were before.[5] The very concern and the very increase in examination of hazards has resulted in improvements to the design and use of many technologies and safety improvements in the workplace. Mining accidents have decreased drastically, many industrial accidents have been reduced, automobile fatalities show signs of decreasing.

Because of the current potentials for risk in our society, and because of the current levels of public concern, there have been a number of efforts to manage risk. There is presently an increasing thrust in Government to manage risks better--more consistently, more realistically, more efficiently. Figure 1 shows the recent growth of legislation in the risk area. Risk management is a very complex area in itself, involving as it does a variety of approaches, legal, legislative, technical, regulatory, market-oriented, etc. While these are not discussed in detail in this report, a short section has been included to indicate briefly some of the major areas of risk management in order to provide a basic understanding of the multiplicity of approaches at present.

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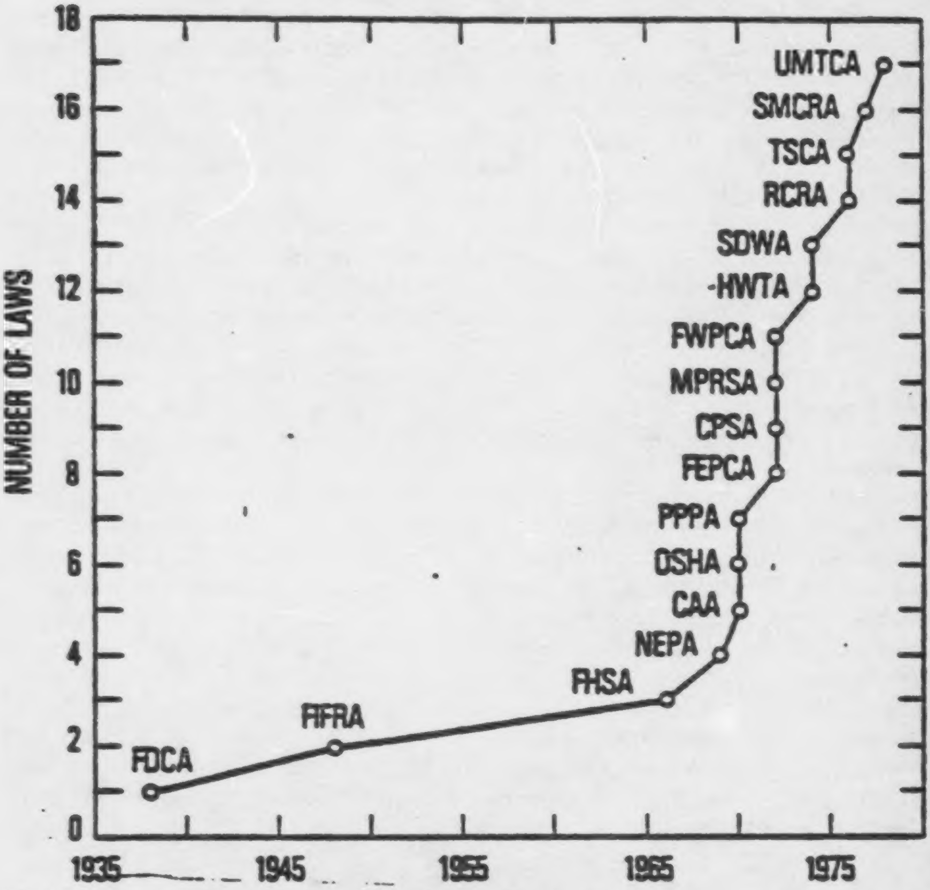
[5] Civiak, Robert L. Society's Attitude Toward Technological Risk, CRS paper, June 29, 1979, p. 3. Robert C. Harriss, et al., Our Hazardous Environment, Environment, v. 20, Sept. 1978, p. 6-41.

FIGURE 1.—HEALTH AND ENVIRONMENTAL PROTECTION LAWS [a]



FDCA — Federal Drug and Cosmetics (1938)
FIFRA — Federal Insecticide, Fungicide, and Rodenticide (1948, 1972, 1975)
FHSA — Federal Hazardous Substances (1966)
NEPA — National Environmental Policy (1969)
PPPA — Poisonious Packaging Prevention (1970)
OSHA — Occupational Safety and Health (1970)
CAA — Clean Air (1970, 1977)
FWPCA — Federal Water Pollution Control (now Clean Water) (1972, 1977)
MPRSA — Marine Protection, Research, and Sanctuaries (1972)
CPSA — Consumer Product Safety (1972)
FEPCA — Federal Environmental Pollution Control (1972)
SDWA — Safe Drinking Water (1974, 1977)
HMTA — Hazardous Materials Transportation (1974)
RCRA — Resource Conservation and Recovery (1976, 1979)
TSCA — Toxic Substance Control (1976)
SMCRA — Surface Mine Control and Reclamation (1977)
UMTCA — Uranium Mill Tailings Control (1978)

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[a] U.S. Congress. House. Committee on Science and Technology. Societal Risks of Energy Systems. Hearing, 97th Congress, 1st Sess., June 18, 1981, Testimony of Chester R. Richmond, p.55.

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REASONS FOR THE CONTROVERSY

A major purpose of this report is to examine and attempt to explain the considerable degree of confusion and controversy that surrounds the whole area of risk assessment, including some of the basic scientific elements. Biological research, for example, would not, at first glance, seem to be a natural source of major controversies. But it is. The evidence of this confusion and controversy is considerable. One research method may show evidence of a risk effect that is not substantiated by other methods, as will be discussed in some detail in this report. Early experimental results based on small sample populations, which may be published for a variety of reasons, may not be statistically meaningful and therefore may not be borne out by research results from later, more comprehensive studies. Scientists frequently disagree on appropriate research methodologies, for example, on what animals to use or what dose levels to employ. Different theories may exist positing different biological effects for a given risk agent. In some cases, the same substance may be shown to be beneficial to human beings in some cases and detrimental in others, even for such commonly used and extensively studied substances as coffee,[6] wine,[7] and other foods.[8] Continuing research and analysis may uncover more and more potential risks–new risks, or evidence of risk agents existing at concentrations that formerly could not be detected–sometimes creating new questions about the safety of substances in wide-spread use, such as saccharin, or of substances previously tested and "proven" harmless, such as Red No. 2 dye, formerly used by the Government to stamp meat products.

A related element of the risk assessment controversy is the different way in which risk is treated in different Government agencies, in different industries, and for different products. Different agencies may assign different "values" to human life in making risk-benefit comparisons. Different industries are subject to different regulations by different Government agencies acting independently of each other, and may operate with different degrees of safety, both to workers and to the public. Different substances are subject to different rules of risk management. In some cases, risk situations that can be regarded as similar are treated in very different ways. All of this tends to raise questions about the purpose, nature, and utility of risk assessment. In this regard, it is not so much the techniques of risk assessment that are called into question, but rather the application of them. Nevertheless, the existence of such disparities in the application of risk assessments tends to raise doubts about the status of knowledge for risk assessment.

Another element important to the controversies over risk assessment lies in the public perception of risks and acceptability to the public of decisionmaking to control those risks. Publicity, special interest groups, and other factors have created, in many areas, public perceptions of risk that may be inconsistent with the scientific findings of risk assessments. For example, people tend to regard air flight as far riskier than it is in fact. Although fatal commercial airline accidents occur infrequently (the last fatal air crash in the United States before the January 13, 1982 Air Florida crash at National Airport involved an Air Wisconsin flight in Valley, Nebraska on June 12, 1980, an interval of 19 months), many people are wary of flying, and flight insurance is sold at airports. Also, public opinion surveys have repeatedly shown that nuclear reactors are widely believed to be capable of exploding like an atomic bomb, even though they physically cannot, and the hazards of nuclear reactors are generally believed to be greater than risk assessments have estimated them to be.[9]

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[6] Carper, Jean. The Puzzling Effects of the Foods We Eat. Washington Post. Sept. 3, 1981. Victor Cohn. Flap Percolates over Effects of Coffee Beans. Washington Post. Aug. 29, 1981.

[7] Thompson, Robert Lewis. A Toast to Good Health and Longer Life. Washington Post. Nov. 12, 1981. Fetal alcohol advisory debated, Science v. 214, Nov. 6, 1981.

[8] Carper, Jean. Food–A Cause or Cure for What Ails Us? Washington Post. Oct. 8, 1981.

People also are apparently willing to expose themselves to different degrees of risk in different situations. The study of the acceptability of various risks to the public is a fairly new area of research.[10] Without examining it closely here, it is clear that individual decisions with regard to taking risks may be based on a variety of factors other than the comparative levels of risk associated with different risk agents that have been established by scientific methods. People's stated perceptions of different risks, as well as their behavior in the face of various risks, are often not consistent with actual relative risks. For example, figure 2 arrays a group of health and safety risks according to their acceptability to, and acceptance by, the public. From this figure, one can see that equivalent levels of risk from different risk agents are regarded very differently by the public in terms of measures of acceptability and acceptance (compare, for example, risk status groups 2 and 4, or 3 and 5).

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[9] Slovic, P., S. Lichtenstein, and B. Fischhoff. Images of Disaster: Perception and Acceptance of Risks from Nuclear Power. In G. Goodman and W. Rowe, eds. Energy Risk Management. London, Academic Press, 1979.

[10] For a further discussion of issues of risk perception and risk acceptability, see for example, Dealing with Risk, ed. Richard E. Griffiths, Halsted Press, Great Britain, 1981; Management of Assessed Risk for Carcinogens, ed. William J. Nicholson, Annals of NY Academy of Science, vol. 363, 1981; Mr. Granger Morgan, Probing the Question of Technology-Induced Risk, IEEE Spectrum, Nov. 1981, p. 58-64; Civiak, Society's Attitude Toward Technological Risk; Steven L. Salem, et al. Issues and Problems in Inferring a Level of Acceptable Risk, Rand R-2561-DOE, Aug. 1980; and Sage, Andrew P. and Elbert B. White. Methodologies for Risk and Hazard Assessment: A Survey and Status Report. IEEE Transactions on Systems, Man, and Cybernetics, v. SMC-10, Aug. 1980. p. 425-446.

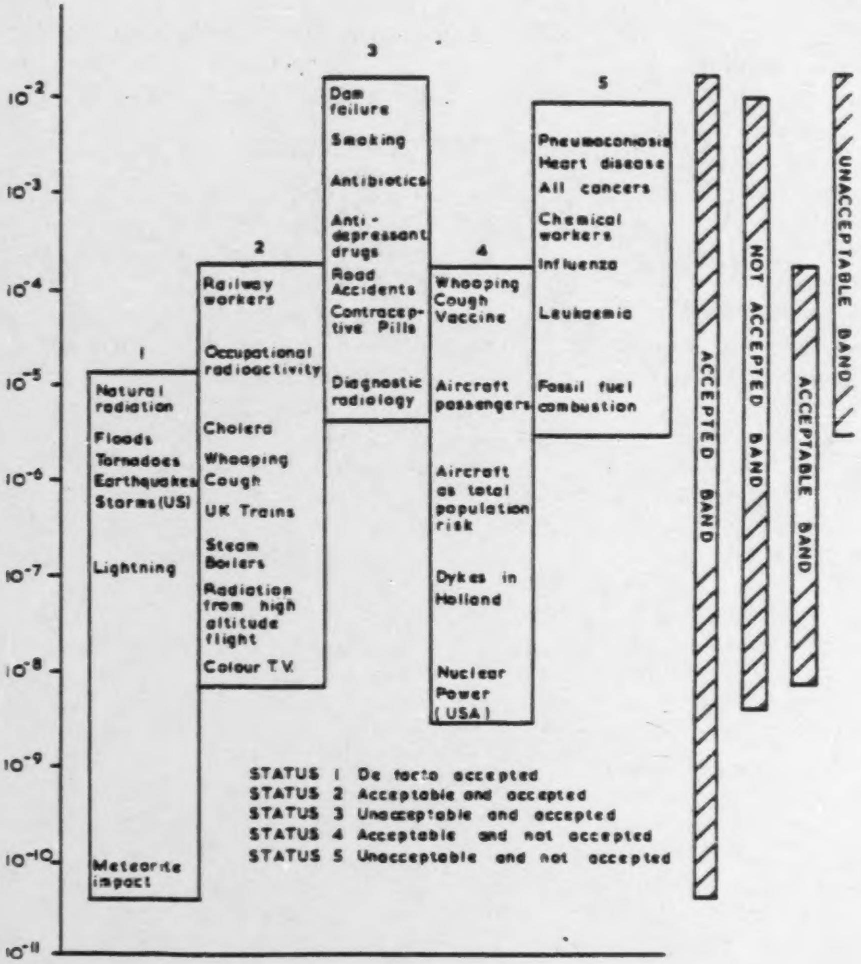

FIGURE 2.—HISTOGRAM OF INDIVIDUAL ANNUAL RISK OF DEATH FOR RISK STATUS 1 TO 5 [a]

Some individuals may accept a higher degree of risk in situations where they have control, or think they do, such as driving an automobile. Individuals also may be willing to inflict a hazard on themselves that they will not accept having imposed on them by society, such as being willing to smoke, but not live near a power plant. Some people may accept a natural hazard, such as lightening or earthquakes as inevitable, and therefore, implicitly acceptable, while they will not accept societally imposed risks of similar magnitudes.[11] Therefore, the appropriate role for risk assessment in decisionmaking, both by individuals and by the Government, is still being developed and debated.[12]

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[a] Comparative risk-acceptability vs. acceptance. Nuclear News, v. 23, Sept. 1980. p. 42. Reprinted from Nuclear and Non-nuclear Risk–an Exercise in Comparability, prepared by the Commission of The European Communities.

[11] Du Pont, Robert L. The Nuclear Power Phobia, Business Week, Sept. 7, 1981, p. 14-16.

All these factors make it important to understand the area of risk assessment at the present time, both for what it can do and for what it cannot do. This report attempts to explain some of the major methodologies that comprise the area of risk assessment, and to examine some of the major issues associated with its use.

ORGANIZATION OF THE REPORT

This report briefly explains each of the major areas associated with risk assessment, including laboratory research, epidemiological studies, systems modeling, modeling of transport processes, and comparative techniques. The report devotes considerable attention to analyzing the possible shortcomings of each technique. The purpose of this focus is not to attempt to prove that the techniques are not of value, but rather to provide some better insight into when they are of value. This is crucial to making informed decisions about the use of risk assessment, and to making informed decisions based on risk assessments. This focus is presented in order to help provide some understanding of when certain techniques can appropriately be used, how much precision and reliability can be expected, what the nature is of any existing controversy surrounding the use of a technique, and what questions should be asked about the research methodology in examining the results of any risk study.

This report first provides an examination of each of the major areas of research that may be used to establish and to quantify cause and effect relationships between risk agents and effects–epidemiological research, animal research, and cellular research. Following this is a separate discussion of two major issues which affect all of these research methods, dose extrapolation techniques and sample size considerations, which are important determinants of the validity of the research results and their applications to specific situations. The report next discusses the types of models that may be employed in conjunction with a risk assessment, and their uses. Following this is a detailed discussion of one type of modeling of major current interest, that is, probabilistic analysis and its role in determining the likelihood of occurence of specific sequences of events that can lead to human exposure to a risk agent in particular cases. Finally, the report discusses the comparative analytical techniques employed in using risk assessment findings for risk management decisionmaking. A concluding section very briefly touches on some of the major elements of risk management in order to indicate how some of the various risk assessment techniques can be applied.

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[12] Although risk assessment is regarded as being a relative newcomer to the world of analysis, some form of risk assessment has been practiced under other names ever since early attempts to regulate steam boiler construction for river boats in the mid nineteenth century.

CHAPTER 2: EPIDEMIOLOGY

INTRODUCTION

Most generally, epidemiology[13] is the branch of medical research which studies the incidence of diseases among groups of people. The primary distinguishing characteristic of epidemiological research is that the induction of the disease is not under the control of the researcher (unless unethical practices are followed). Rather, the researcher is limited to the study of disease cases which occur naturally or accidentally. Epidemiological research includes population studies of diseases or other human health impacts which are induced by biological, chemical, and physical risk agents. While epidemiology has been a valuable tool for detecting patterns of risk and establishing statistically significant associations with risk agents, it cannot demonstrate cause and effect.

Whether because of ignorance, accident or deliberate design, some group of humans has been exposed to each of virtually all risk agents of current concern. Therefore, there is considerable opportunity to use epidemiological research methods in risk assessment, and epidemiological studies have contributed significantly to our understanding of risks. A recent study of 26 chemical substances or processes identified to be responsible for cancer in humans indicated that the carcinogenicity was first identified by epidemiological evidence for 20 of these.[14] Consequently, it is important to understand both the utility and the limitations of this widely used tool of risk assessment.

Because direct experimentation on humans is largely constrained by legal and ethical factors for substances known or expected to be harmful to humans, the particular importance of epidemiological research is that it is generally the only means available for obtaining information that directly identifies the effects on humans of a given risk agent. Some drug research has been done using consenting prison inmates or terminally-ill medical patients, but this research was usually limited to drugs being tested for beneficial effects and therefore includes only a small fraction of risk agents of concern, and has now been terminated. Furthermore, the extrapolation from terminally ill patients or other specialized population groups to the general population may not always be valid, since susceptibility to risk agents may vary with physical condition (e.g., health), demographic characteristics, or synergistic factors, as described in this chapter.

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[13] From the Greek, "epi," in, and "demos," people.

[14] Tomatis, L., C. Agthe, H. Bartsch, J. Huff, R. Montesano, R. Saracci, E. Walker, and J. Wilbourn. Evaluation of the Carcinogenicity of Chemicals: A Review of the Monograph Program of the International Agency for Research in Cancer (1971-1977). Cancer Res., v. 38, p. 877-885, 1978.

Several types of epidemiological evidence are used in the discovery of risk-related responses in humans. These include:

> Biological or biochemical response directly related to duration and dose of exposure;
>
> Disease incidence or mortality differences related to occupational exposure;
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> Disease incidence or mortality differences between geographic and socioeconomic regions (i.e., environmental);
>
> Time trends in disease incidence or mortality related to either the introduction or removal of a specific agent;
>
> Retrospective-prospective and prospective studies of the consequences of human exposure;
>
> Clinical case reports (particularly in early stages).

Two main types of epidemiological studies are used to establish evidence of a risk: cohort studies and case-control studies. Epidemiological cohort studies involve the comparison of groups differently exposed to a substance (i.e., without preselection according to state of health). The comparison may involve: (a) totally unexposed *versus* exposed groups; (b) groups having distinctly different levels of exposure; or (c) rates in exposed groups *versus* the rates prevailing in the general population. Epidemiological case-control studies involve the comparison of people with a given disease *versus* people without the disease (i.e., without preselection according to exposure to a given risk). For either type of study, the groups must be otherwise comparable with respect to appropriate demographic variables (age, sex, race, etc.) to ascertain if these factors affect the relationship between exposure and risk for the hazard under investigation.[15]

The chief limitation of epidemiological research is the lack of research control over the experimental parameters, coupled with the "complexity of social systems and the heterogeneity of the human species."[16] Epidemiological research is characterized by the fact that the researcher does not directly select or control any of the critical parameters of the situation–the population size exposed, the selection of individuals to meet certain criteria (age distribution, etc.), the total exposure, the dose rate, or other environmental or dietary exposures.

Shell Oil Company, in a recent issue of its *Ecolibrium* magazine, has identified some of the major limitations of the use of epidemiology for risk assessment:

> Epidemiology has four major drawbacks: first, possibilities usually can be established only after people have contracted the disease; second, the information is available only long after the causative factor has operated; third, multiple exposures on and off the job interfere with the ability to make neat cause-and-effect judgments; and fourth, epidemiology can be insensitive–effects often cannot be detected at the low levels of incidence for which industry is striving.[17]

The most a researcher can do is identify the parameters and select among available data, and often the available data is too limited to allow much selection. The significance of these limitations is outlined below.

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[15] Scientific Bases for Identifying Potential Carcinogens and Estimating Their Risks. Interagency Regulatory Liaison Group (IRLG), Work Group on Risk Assessment, Feb. 6, 1979, p. 18-19.

[16] MacMahon, Brian. In Pursuit of Public Health, Technology Review, v. 84, Nov.-Dec. 1981, p. 50-60.

[17] As quoted in Occupational Risk: A Proof-Disproof Minuet, Technology Review, v. 83, p. 92-93, Apr. 1981.

Additional limitations, with particular regard to case-control studies, are discussed in a recent article reviewing the use of medical records in epidemiology. According to this article, case-control studies are "replete with methodological complexities":

> The selection of an appropriate group of controls is by no means straightforward; several biases may be introduced in the process. Control subjects (particularly those from other services at the same hospital) often have characteristics related to their being sick that systematically affect their chances of having the exposure under investigation. To overcome such difficulties it is almost always necessary to exclude certain groups of control subjects; the criteria for exclusion are rarely unambiguous. Moreover, the selection of different groups of controls generally gives rise to quite different estimates of risk. Case control studies also cannot provide an estimate of the base-line incidence or prevalence of a disease, only an estimate of the relative levels of risk among exposed and unexposed patients.[18]

A review of the use of epidemiology in studies of air pollution effects points to still other factors:

> Most epidemiologists compare the health of the citizens of several cities with very different air qualities. Yet people in different cities also have different age patterns, smoking habits, eating habits, occupational hazards, water supplies, income levels, and educational patterns--all of which are known to affect human health as much as or more than air pollution. Subtracting out the effects of such "confounding factors" to identify the effects of air pollution is difficult.[19]

CORROBORATION OF EXPOSURE

One of the most basic problems encountered in epidemiological studies is simply reliable corroboration of an individual's exposure to an event. Frequently, because of the passage of time, this is not as simple, unambiguous a step as it would seem to be, as both memories and records may prove faulty for purposes of rigorous scientific investigation.

Memories

Personal accounts are often a primary means of establishing individual histories with regard to exposure to a risk agent. However, with job and residential mobility, personal accounts have often been found to be inaccurate as to dates and other critical information.

Even greater problems are encountered when studies depend upon information supplied by survivors of study subjects. For example, in a printed comment on Narajian's study of naval shipyard workers, a relative of a naval shipyard worker pointed out that many next-of-kin do not know the exact nature of their relative's work:

> Being the son of a shipyard worker, I am skeptical. I was unaware for all these 20 years of whether my father did or did not work in a nuclear-related area, or whether he wore a radiation film badge; and so were others in my immediate family. I only know that he spoke every evening about the nuclear-powered submarines he was working on. I finally discovered last spring that he does not work in "nuclear-related" areas and does not use a film badge. My notions were wrong all these years, and I must assume that many other kin are equally unaware of the true facts on this matter. When confronted with questions about radiation exposure and the

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[18] Kurland, Leonard T. and Craig A. Molgaard. The Patient Record in Epidemiology. Scientific American, v. 245, Oct. 1981, p. 54-63.

[19] Improving studies of Public Health, E-Lab, Apr.-June 1981, p. 1.

knowledge that one's relative died of cancer, next-of-kin may naturally assume, "yes, he worked in nuclear."[20]

Other causes of inaccuracies of personal recollections, aside from lack of information, are speculative, but could include: personal convictions about the cause of death of a loved one; faultier memories among a "control" group not suffering the risk; anticipation of some monetary restitution for persons legitimately affected by the risk agent; or merely forgetting of details over time. In fact, a subsequent review of the dosimetry data for the naval shipyard workers did indeed show that, of the leukemia victims identified in this study who were reputed to have been radiation workers, only half (3 out of 6) had any record of radiation exposure.[21]

Records

While records in most cases provide far more detailed and reliable information than memories, these too are often inadequate for investigative studies.[22]

A major problem encountered by researchers is the problem of missing documentation, either for individual cases or whole groups of people. Many employment and medical records have been destroyed by fires or other such incidents, discarded when their apparent usefulness had ended, filed in a forgotten location, or misfiled. Even records which have been recovered can be incomplete or inconsistent, with different records showing discrepancies as to dates, exposures, treatments, and other critical information, either because of a failure of the original record-keeping procedures, or because of subsequent mishandling of files. Of course, the capabilities of modern computers to store and sort data may simplify the record-keeping aspects of epidemiological studies in the future.

Records can also be inconsistent--or even consistently wrong--due to deliberate falsifications by any party contributing to the record. For example, employees may lie about past health history or risk exposures to obtain a job; or employers, or individuals in a company, may falsify exposure records to avoid fines, shutdowns, bad publicity, or increased operating costs.

Most often, however, the records simply contain insufficient detail for epidemiological purposes. That is, records kept for employment or other purposes may not have collected the data that an epidemiologist needs to verify level of exposure, etc.

Another potential difficulty may lie in obtaining access to data, for such reasons as personal privacy and corporate proprietary concerns. Concerns about individual privacy have recently led to new laws which explicitly restrict organizations such as medical institutions, educational institutions, and employers from providing or disseminating certain types of information on individuals that would violate their rights to privacy. Much of the health information that would be vital to an epidemiological study falls into the categories protected by these laws. Lack of access to large portions of a potential data base further exacerbates any problems of inadequate sample size, and may also introduce biases in the study, because the willingness to permit access to data may be correlated with certain types of performance (for example, if examination of the data would reveal illegal activity).

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[20] Dube, Donald A. Letter to the Editor. Technology Review, v. 81, Feb. 1979, p. 8-9.

[21] Cohen, Bernard L. The Cancer Risk from Low-Level Radiation. Health Physics, v. 39, p. 671 (1980).

[22] Inadequacies of records for purposes of epidemiological research are referred to in several sources. See for example: IRLG Study, p. 20. See also the discussion below on individual dose monitoring.

DOSE DETERMINATION

Any study of a risk agent must correlate disease incidence or other effects with dose levels of the risk agent. In the case of epidemiological research, this can be particularly difficult because the researcher cannot control the exposure levels. In fact, epidemiological studies are often conducted long after the exposure actually took place. Some of the impacts of dose determination on the results of epidemiological studies are illustrated by the recent controversy regarding a reinterpretation of the data on Japanese atomic bomb survivors.[23]

There are several indirect techniques used to arrive at estimated exposure levels appropriate for use in epidemiological studies. Two of these, individual dose monitoring and site dose monitoring, require actual measurements to be made at the time of exposure. Several other techniques provide ways to construct estimates of exposure based on theoretical formulations or on data available after the actual exposure occurred. These techniques include calculations based on exposure time, measurement of coexisting or decay substances, and measurement of material deposition in human or animal tissue. Each of these techniques has certain appropriate and useful applications and certain limitations which will be discussed.

Individual Dose Monitoring

The most accurate dose information derives from situations in which the exposed individuals are routinely monitored for the risk agent in question. This situation prevails in certain very specific occupational settings. This is the case, for example, for radiation workers, who carry dosimeters, film badges or other radiation sensitive devices to monitor their exposures. However, even this system has possible drawbacks if procedures controlling the use of such monitors are not stringent, in that individuals may forget to wear their monitors or monitors may deliberately or advertantly be switched between individuals. Narajian lists several possible shortcomings of radiation dose monitoring:

> Perhaps workers exposed to radiation from nuclear power plants or from fission products generated by these plants receive contamination from a particular isotope (such as plutonium) in such minute quantities that its detection in nuclear workers is overlooked by the current methods of measuring radioactive contamination in these workers.
>
> Nuclear workers may be receiving more radiation than the records at one plant indicate: workers might swap radiation badges in order to qualify for overtime work; a nuclear worker might become overexposed by traveling from one plant to another and receiving his maximum quota for a three or six month period at each plant in just one week; radiation accidents might be inaccurately reflected by the

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[23] For further discussions of this issue, see for example: Elliot Marshall, "New A-Bomb Studies Alter Radiation Estimates", Science, May 22, 1981, pp. 900-903; William J. Schull, et.al., Genetic Effects of the Atomic Bombs: A Reappraisal, Science, v. 213, Sept. 11, 1981.

badge reading or incorrectly recorded in official records; radiation to the arms or legs could be much higher than badge readings, because badges are located on the chest; or deposition of internal emitters may be contributing to a higher effective Rem count than current estimates allow. (Dr. Mancuso's study excluded internal contamination as measured by urine counts for radiation and total body counts for radiation as the sole cause of excess cancer in his study, but the possibility remains that internal emitters played a part in increased cancer risk.) [24]

Site Dose Monitoring

Site monitoring techniques involve actual measurements of the dose levels as well, but in this case the measurements are not specifically for individuals, but rather are for locations. This is clearly a more practical technique to use when areas and/or numbers of people exposed are large. In this case, individuals may move between locations covered by different monitors, or may occupy areas beween monitors, so careful processing of the data is required to map the dosage over a whole area from the data available from the monitored point sites, and to accurately determine dosages to individuals based on the site measurements and their pattern of movement between sites.

Where appropriate, the extrapolations from monitored point sites must be corrected for weather or topological features (see below). Site dose monitoring is particularly practical in cases where the risk agent release is either routine, as in the case of monitoring for regional air pollution indices, or where the release occurs over a sufficient period of time to allow a monitoring system to be established, as in the case of fallout from nuclear weapons testing.

Another concern relates to the often sizeable variation of certain environmental risk agents, such as air pollutants, over time. The concern here is not so much with the accuracy of the measurement as it is with the validity of the time period used for reporting and comparing data. As table 3 indicates, there is often little correlation between maximum and minimum readings; that is, it may be erroneous to characterize a city as the most polluted based on the relative maximum readings, when the rank order of the relative minimums may be very different. In one experiment, researchers found that some of the dirtiest areas on the 24-hour maximum list were cleanest on the 8-hour maximum list:

> Those differences are due both to the sources and to the patterns of pollutant emissions. Near a generator, the environment may be dirty for 8 hours and clean for 16; thus it may be relatively "dirty" based on the 8-hour maximum but relatively "clean" based on the 24-hour maximum.[25]

The impacts of these differences in pollution levels on different time scales may be critical because, as is the case with cigarette smokers, sufficient low pollution periods could actually counteract some of the harmful effects of high pollution periods.[26] Therefore, selecting a particular dose measurement interval, or in other cases, selecting particular sites or measurements, can bias the results of a study.

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[24] Thomes Narajian, The Controversy over the Health Effects of Radiation, Technology Review, v. 81, Nov. 1978, p. 74-82.

[25] Improving Studies of Public Health, E-Lab Apr.-June 1981, p. 2.

[26] Ibid.

TABLE 3. COMPARABILITY OF DIFFERENT AIR POLLUTION INDICES [a]

Selected districts	Ranked according to			
	24-hour maximum, SO_2, 1978	24-hour minimum, SO_2, 1978	24-hour maximum, SO_2, 1975	24-hour maximum, TSP, 1978
Burrell	7	22	3	25
Gastown	20	3	19	29
Girty	8	23	4	26
North Armstrong	1	9	7	30
South Armstrong	14	24	9	33
Indiana	15	4	13	31
Black Lick	35	17	1	24
Blairsville	34	27	17	9
Buffington	24	28	2	35
Clyde	26	34	34	4

[a] Ibid., p. 1.

Note. Comparative numerical rankings of selected Pennsylvania districts using different air pollution indices. The first column shows rankings according to maximum average sulfur dioxide (SO_2) levels period of 1978; the second column shows rankings according to minimum 24-hour averages. There is clearly no correlation between those two measures. A comparison of the first and third columns shows the extent to which pollution levels vary from year to year, while the fourth column shows the effect of using total suspended particulates (TSP) instead of SO_2 as the measured pollutant.

Theoretical Dose Estimates

Gross estimates of dose received can sometimes be based on calculated estimates of dose levels and durations of exposure. Such estimates, of course, are only as good at the ability to compute the dose rates and the knowledge of the duration of exposure. In the absence of other information, such methods can provide a reasonable, although necessarily approximate, indication of exposure level. Particular use can be made of such techniques in the case of situations where monitoring procedures and equipment are not available, for example, in the case of studies of radiation effects on Japanese atomic bomb survivors,[27] or in conducting predictive studies for such events.[28]

Dose distributions over an area are affected both by the distribution mechanism (such as an explosion) and by the presence of manmade or natural topological features, localized weather phenomena, etc. Models of these features and phenomena can be applied to determine how they affect the spread or impact of the risk agent. However, in a number of cases, the complex physical and chemical phenomena involved in determining the interactions of risk agents with the environment are not completely understood. Therefore, in some cases, such as in modeling of the impacts of chloro-fluoro-carbons on the ozone layer of the atmosphere, or in modeling the effects of carbon dioxide on long-term climate variations,[29] the relevant models and their results are subject to dispute.

Deposition Measurements

The total exposure can often be established from tissue samples from exposed organisms, human and other. Such techniques require accurate understanding of the preferential biological absorption and retention of certain substances in particular organs or organisms–strontium in bone, iodine in the thyroid, mercury in fish, for example–as well as knowledge of any physical decay processes of the hazardous material, such as radioactive decay or biodegradation. Such tissue sampling can sometimes be conducted on living organisms–testing hair and nail clippings for arsenic, for example–but in some cases is accomplished after death or amputation, as in the case of the tests of bone samples from radium watch dial painters.

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[27] Studies revise dose estimates of A-bomb survivors. Physics Today, v. 34, p. 17-20 (Sept. 1981) and Beebe, Gilbert W. The Atomic Bomb Survivors and the Problem of Low Dose Radiation Effects. J. of Epidemiology, v. 114, Dec. 1981. p. 761-783.

[28] Fetter, Steven A. and Kosta Tsipis. Catastrophic Releases of Radioactivity, Scientific American, v. 244, Apr. 1981, p. 41-48.

[29] Carbon Dioxide and Climate: A Scientific Assessment, National Academy of Sciences, 1979.

Associated Substances

A risk agent may sometimes be associated with other substances, which may or may not also be risk agents. The related substance can either be coexistent, be a byproduct, or be a product of any transformation the material undergoes, such as biodegradation or radioactive decay. Such associated substances, together with information about their relationships to the risk agent of interest, can be used to provide a measure of the concentration of the substance of interest. In the case of radioactivity, for example, activation or decay products can often provide such a surrogate monitor; [30] in the case of air pollution, sulfur dioxide (SO_2) concentrations have often been used in epidemiological studstudies as an indicator of the level of other pollutants.[31]

The validity of this technique requires that the amount of the associated material has not increased (due to accumulation from other sources) or decreased (due to materials transport) since the exposure incident, and that other factors, such as technological developments or regulatory requirements, have not altered historical relationships. For example, the relative concentrations of SO_2 and other air pollutants have changed since the U.S. Government imposed restrictions on SO_2 measurements in 1970.[32] Table 3 includes a comparison between SO_2 and suspended particulate rankings which demonstrates the lack of correlation between the two pollutant levels.

DOSE LEVELS

Dose levels, of course, cannot explicitly be controlled in epidemiological studies. Therefore, the doses may not always be at levels of greatest concern, and impacts at other levels may have to be extrapolated. In particular, exposures that result from accidents may often be considerably larger than chronic low-level emissions that may be the primary concern for the general population. Also, in cases where the effects of low doses are very small, the only incidents which can be studied successfully may involve much larger doses. Thus, knowledge about radiation effects is dominated by studies of groups which experienced large exposures, including Japanese atomic bomb survivors, Marshall islanders exposed to fallout from nuclear weapons tests, radium watch dial painters, several groups exposed to X-rays or radioactive chemicals for medical treatment, and several groups of miners,[33] whereas the major concern at present is over effects at very low doses. Table 4 summarizes the findings of some of the major studies of high level radiation exposure. By contrast to these studies, which examined people exposed to hundreds or thousands or rems,[34] the low level doses of concern are in the range of a few rem or less.

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[30] Kerr, George D. Findings of a Recent ORNL Review of Dosimetry for the Japanese Atomic Bomb Survivors. ORNL/TM-8078, Sept. 1981. 70 p.

[31] E-Lab, p. 2.

[32] E-Lab, p. 2.

TABLE 4. SOURCES OF INFORMATION ON CANCER FROM RADIATION [a]

Type of cancer	Cause of exposure or X-ray treatments	Exposure date	Years after exposure considered	Number of subjects	Average dose (rem)	Cases observed	Cases expected	Cases 10^6 rem yr
Leukemia	A-bombs, Japan	1945	5-25	23,979	130	81	19.7	1.0
	Spondylitis	1935-54	0-25	14,554	372	52	5.5	0.9
	Menorrhagia	1940-60	0-24	2,000	136	6	1.3	1.2
Bone	Ra^{226}intake	1915-35	11-56	775	17,000	48	0.4	0.11
	Ra^{224}treatments	1944-64	4-25	925	4,410	45	0.12	0.84
	Spondylitis	1935-54	6-27	14,654	372	4	0.63	0.10
Breast	A-bombs, Japan	1945	16-25	12,000	125	26	12.9	0.9
	Fluoroscopy	1940-49	10-30	243	121	(22)	(4)	8.4
	Mastitis		10-29	606	200	11	4.2	6.0
Lung	Uranium mines	1920-63	6-50	4,146	4,680	135	16	0.53
	Fluorspar mines	1935-63	11-33	800	2,770	51	2.8	1.6
	Metal mines		16-37	1,759	1,720	45	16	0.67
	Spondylitis	1935-54	6-27	14,554	400	96	54	1.2
	A-bombs, Japan	1945	16-25	19,472	133	71	57	0.60
Gastro-intestinal	A-bombs, Japan	1945	25	23,979	130	378	363	0.52
	Spondylitis	1935-54	11	14,554	375	53	34	0.81
Leukemia, ages 0-9	A-bombs, Japan	1945	6-24	4,507	112	19	2.9	1.6
	Thymus X-rays	1926-57	0-35	1,451	65	6	1.0	3.0
	Tinia capitis	1940-49	0-22	2,043	30	4	0.9	3.4

[a] Cohen, Cancer Risk, p. 660. Based on data from The Effects on Population of Exposures to Low Levels of Ionizing Radiation, Washington, National Academy of Sciences, 1972.

POPULATION COMPOSITION

One sometimes important consideration of epidemiological studies is the nature of the exposed population. Epidemiological studies, by their nature, permit restricted or limited control over the selection of subjects for experimentation, and quite often, the population groups represented in such a study are not typical of the general population. Worker populations, for example, may not be completely typical of the general population, or other demographic differences or synergistic effects can affect research results. The size of the group available for study may also be a research limitation. The importance of such differences varies, but care must be exercised in extrapolating study results involving groups which differ demographically from the overall population.

Healthy Worker Effect

One of the most productive sources for epidemiological studies involves various worker populations. The reason for this is that workers are often exposed to a hazard more persistently and over a longer time period than members of the general population, better documentation is often available verifying the nature and degree of exposure, and workers are sometimes exposed to substances which do not routinely enter the public environment. Table 5 provides a partial list of the variety of occupations in which workers are apparently exposed to cancer-causing substances, and recent articles have detailed research findings linking various diseases to occupational exposures.[35]

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[33] Cohen, Bernard L. Cancer Risk, p. 659-60.

[34] A rem (roentgen-equivalent man), is a measure of deposition of radiation in tissue that normalizes for different energies and types of radiation.

Worker exposure can occur either because of ignorance of a substance's effects (as has probably been the case historically for most substances in the early stages of their use), because of accidents, because standards set for workers allow for specified levels of exposure (as in the case of radiation where allowable dose levels are in excess of those for the general population, but limits are strictly specified and monitoring procedures and other controls are established[36]), or because of carelessness or even deliberate wrongdoing on the part of both management and workers in following standards.

TABLE 5. SAMPLE OCCUPATIONAL GROUPS HAVING APPARENTLY OCCUPATIONALLY LINKED CANCERS[a]

Occupational groups	Cancer Sites (percent excess reported)
Coal miners	Stomach (40).
Chemists	Pancreas (64); Lymphomas (79).
Foundry workers	Lung (50-150).
Textile workers	Mouth and pharynx (77).
Press operators (newspapers)	Mouth and pharynx (125).
Metal miners	Lung (200).
Coke byproduct workers	Large intestine (181); Pancreas (312).
Cadmium production workers	Lung (135); Prostate (248).
Rubber industry:	
Processing	Stomach (80); Leukemia (140).
Tire building	Bladder (88); Brain (90).
Tire curing	Lung (61).
Furniture workers	Nasal cavity and sinuses (300-400).
Shoe workers	Nasal cavity and sinuses (700).
Leather workers	Bladder (150).

[a] Occupational Risk: A Proof-Disproof Minuet, Technology Review, v. 83, Apr. 1981, p. 92-3, based on data from K. Bridbord, and others. Estimates of the Fraction of Cancer in the United States Related to Occupat Factors. Washington, Health, Education and Welfare. U.S. Dept. of HEW, 1978.

A significant concern in interpreting the results of epidemiological studies involving workers and in extrapolating those results to the general population is that workers, as a group, are not typical of the general population in terms of health. Workers tend, as a group, to be healthier than the general population. This leads to several seemingly paradoxical consequences, often known as the *healthy worker effect*.

First, diseases with long incubation periods, such as cancer, can appear to have a greater incidence among workers than among an identically exposed general population sample because fewer workers will succumb to other chronic medical illnesses and injuries during a given time period than will individuals from the general population. That is, the greater incidence of other medical conditions in a general population sample may kill individuals who, had they survived, would have contracted cancer. Therefore, an extrapolation of an epidemiological study from a worker group to the general population must be corrected for differences in the death rates due to other causes between the two groups. This effect is part of the cause for debate in the Mancuso study of radiation workers.[37]

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[35] See for example, Devra Dee Davis, Cancer in the Workplace, the Case for Prevention, Environment, July-Aug. 1981.

[36] As specified in 10 CFR, part 20.

Even in the shorter term, the lower base rates of incidence of many illnesses among workers may make it difficult to compare the risk-agent induced change in illnesses to that in the general population. In particular, there is evidence regarding enhanced susceptibility of asthmatics to pulmonary dysfunction resulting from air pollution incidents,[38] and severely afflicted asthmatics may be unable to work and may therefore not be equally represented in the worker and general populations.

On the other hand, another consideration when examining worker populations is that their better overall health may provide for greater resistance to, or enhanced rates of recuperation from, certain diseases. If this is true of a risk agent induced disease, this factor would tend to underestimate the impacts of the risk to the general population based on data from workers. Little data is available on such a phenomenon, and it is not clear whether, or to what extent, this would counteract other worker-related effects.

Demographic Characteristics

Aside from the healthy worker effect, epidemiological studies may have shortcomings as indicators of risk to the general population simply because the exposed population differs demographically from the general population. A worker population, for example, would not have an age distribution typical of the general population, and might also not represent the sexes in the same proportions as the general population. A study of people in a particular geographical region may have dietary, environmental, or ethnic differences from the general population of interest. Such differences may affect the results of risk studies. However, in many cases, a completely appropriate population sample simply isn't available, and in the field of epidemiology, researchers cannot compensate experimentally for gaps in the data base (although they may be able to compensate statistically).

POPULATION MOBILITY

Mobility patterns for the population group of interest are another important concern in epidemiological studies. People who move away from a job or a geographical area may become unavailable for purposes of certain studies--for example, where interviews or follow-up medical procedures are required--thus reducing the size of the potential data base. People move into given geographical areas as well, so any study which seeks to correlate past risk-producing events with long-term consequences must identify with certainty that members of the population who contracted a certain disease were in fact residents in the time period of concern. This requires additional data collection and processing, and may be difficult in cases where epidemiological research is conducted through such devices as medical records, as these may not record dates of residence in an area.

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[37] Cohen, Bernard L. Cancer Risk, p. 668 and T. Narajian. Controversy over Health Effects, p. 81.

[38] See, for example, Marge Kennedy. Witness takes on Hart over the "lunacy" of no-risk standards for air pollution, the Energy Daily, v. 9, June 10, 1981, p. 2.

Synergistic Effects

There is a substantial and growing body of evidence available to support a claim that, for certain risk agents, the impact varies considerably depending on the exposure of the population group to other risk agents, dietary habits, etc. Thus, the risk of asbestos to asbestos workers or birth control pills to women has been found to be greater among those exposed individuals who also smoke (see table 6), although in certain cases, for example, for radon exposures, the apparent synergism between radon and smoking has been disputed.[39] Synergistic effects may operate through a number of mechanisms, including:

-alteration of the uptake and/or distribution of the risk agent;
-modification of the metabolic activation of the risk agent;
-enhancement of the susceptibility of target tissues; and
-acceleration of tissue reactivity.

Such mechanisms may be specific for particular organs or conditions of exposure.[40]

TABLE 6. ESTIMATED ANNUAL MORTALITY RATE PER 100,000 WOMEN FROM MYOCARDIAL INFARCTION BY USE OF ORAL CONTRACEPTIVES, SMOKING HABITS, AND AGE (IN YEARS)[a]

Smoking habits	Myocardial Infarction			
	Women aged 30-39		Women aged 40-44	
	Users	Nonusers	Users	Nonusers
All smokers	10.2	2.6	62.0	15.9
Heavy *	13.0	5.1	78.7	31.3
Light	4.7	.9	28.6	5.7
Nonsmokers	1.8	1.2	10.7	7.4
Smokers and nonsmokers	5.4	1.9	32.8	11.7

[a] Physician's Desk Reference, v. 35, Medical Economics Co., 1981. p. 1767. From Jain, A.K. Studies in Family Planning, v. 8, p. 50, 1977.
* Heavy smoker: 15 or more cigarettes per day.

Therefore, considerable care must be taken in interpreting the results of epidemiological studies to identify other factors–dietary, environmental, occupational, habits, etc.–which may enhance the apparent degree of risk from a given risk agent.

Sample Size

In epidemiological research, as in other forms of risk research, the size of the population that can be included in a study is often a critical limiting factor of the study. Epidemiological studies, of course, are often limited entirely by the population which has been exposed, and which can be identified (and, if necessary, induced to cooperate). In some cases, fairly large populations have been exposed–for example, millions of people in the case of many widely distributed drugs, such as aspirin and birth control pills. In other cases, exposed populations may be very small. Table 4 shows that some radiation studies have involved only a few hundred people. The significance of sample size in the interpretation of results will be discussed in Chapter 6.

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[39] Cohen. Cancer Risk. p. 666.
[40] IRLG Study, p. 14.

CHAPTER 3: ANIMAL RESEARCH

INTRODUCTION

A great deal of what is known or suspected about the effects of various risk agents on humans has been learned through experiments on animals. Animal research allows a degree of experimental control rarely possible with humans, although concerns about the treatment of laboratory animals in experiments and under general laboratory practices could affect research possibilities in the future.[41]

The major benefit of animal research is that critical experimental factors, such as dose, can be varied in a systematic way to perform scientifically rigorous studies. Thus, studies are often able to identify trends of effect in some detail. In addition, experimental results can be replicated to confirm validity or to assure the elimination of extraneous factors. Scientific theories can be tested by the specific selection of test parameters.

On the other hand, there is always concern over the detailed comparability of the results of research on animals to human experience. Even though a great deal of research has been done to validate test animals and experimental techniques used, the complexity of biological organisms and biochemical interactions requires continuing experimentation to verify the test animals and techniques for each new risk agent. The case of thalidomide is perhaps one of the most prominent examples of a situation in which animal research provided no indication of the risk that existed for humans.[42]

A variety of species have been used as test animals for laboratory risk research studies. Much of this variety is due to the requirements of biological comparability (see next section for further detail). However, the choice of test animals is, for practical reasons, also dictated by such factors as cost, ease of care, shortness of life span, ease of breeding, ease of handling in large numbers, and genetic homogeneity (i.e., inbred strains). That is why small rodents–mice, rats, and hamsters–are most often used for these studies, although many other mammals, including dogs, pigs, monkeys, and others, have also been used, as specific cases require and practical considerations permit.[43]

Animal research encompasses studies of the animals both before and after death. Studies conducted while the animals are still alive include observations of such factors as size, weight, condition of external features (skin, hair, eyes, etc.), gross evidence of internal abnormalities (as bone formation), reproductive capacity (including fertility, reproductive frequency, litter size, changes in frequency of spontaneous abortion or live births, and other abnormalities), lifespan, behavior (food intake, sleep habits, aggressiveness, problem-solving ability, etc.), body functions, and genetic changes (as evidenced by characteristics of subsequent generations). After death, additional information can often be obtained through detailed gross pathological examinations to discern the specific cause of death and the nature and extent of any internal morphological abnormalities (such as tumors) in each of the internal organs, and through microscopic examinations of tissue samples for histologic abnormalities.

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[41] Holden, Constance. Revised Animal Bill Under Scrutiny. Science, v. 216, June 4, 1982, p. 1084-5.

[42] U.S. Congress. House. Committee on Science and Technology, Subcommittee on Science, Research, and Technology. 96th Congress, 1st Sess. Technical Information for Congress. July 1977. p. 418.

[43] IRLG Study, p. 24-5.

BIOLOGICAL SPECIFICITY

One of the greatest difficulties in laboratory studies involving animals is determining the specificity of a particular risk consequence to the experimental animal, or even the organ, tested. Risk agents may produce similar consequences over a wide range of life forms, may be specific to a certain type or class of animal, may produce different effects in different animals, may produce an effect to a different degree in different animals, or may produce an effect only on a specific organ or type of tissue. Table 7 lists agents which are known to be essential to human life, but which have been found to be carcinogenic in at least one animal species, in some cases human beings.

A great deal of study has been done to try to correlate results of experiments with animals to human experience, but because of the complexity of risk agent responses, it is difficult to draw overall conclusions about whether experimental results are predictors of human risk. For example, certain aflatoxins are strongly carcinogenic in rats but are ineffective in several strains of adult mice; beta-naphthylamine is carcinogenic for humans, dogs, and several other species but has not produced tumors in rats; dimethylnitrosamine has been found to be carcinogenic in many strains of vertebrates.[44] Table 8 shows, for a number of risk agents, the species specificity for various test animals.

TABLE 7. COMPOUNDS ESSENTIAL TO HUMAN LIFE BUT CARCINOGENIC TO AT LEAST ONE ANIMAL SPECIES [a]

Compound	Role in Human Health	Postive Tumor Species
Chromium	Essential nutrient in low concentrations for fat synthesis	Human, rabbit, rat.
Nickel	Essential nutrient in low concentrations	Human, rat, cat, hamster, mouse
Progesterone	Steroid hormone essential to sustaining normal pregnancy	Mouse.
Selenium	Essential nutrient in low concentrations for tissue respiration	Rat.
Testosterone	Steroid hormone responsible for masculine characteristics	Mouse.

[a] Management of Assessed Risk for Carcinogens, Ed. William J. Nicholson, Annals of New York Academy of Sciences, v. 363, 1981. p. 54.

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[44] IRLG Study, p. 15.

TABLE 8. SPECIES SPECIFICITY [a]

Compound	Positive Tumor Species	Nonpositive Tumor Species
Captan	Mice	Rats.
DDT	Mice	Rats, hamsters, dogs.
Dieldrin	Mice	Rats.
Formaldehyde	Rats	Mice.
N-Acetylaminofluorene	Mice	Guinea pigs.
2-Naphthylamine	Dogs, monkeys, hamsters	Rats, rabbits.
Phenobarbital	Rats, mice	Humans.
Pronamide	Mice	Rats, dogs.

[a] Ibid., 53.

The organs and tissues which are the targets of risk agents may also vary in different species and even under different exposure conditions. Some agents attack widely different target sites in different species (e.g., benzidine induces bladder carcinoma in humans, and cholangiomas and liver cell carcinomas in hamsters and rats) while other agents produce closely similar responses for a variety of life forms (e.g., vinyl chloride induces the same type of angiosarcomas of the liver in humans, rats and mice). [45] Such variability in the action of substances can be due to inherent differences in susceptibility among different species, differences in biological or biochemical pathways, or variability in the reactivities of individual agents.[46]

The belief that there are qualitative correlations between experimental disease incidence in animals and human risk has been a major factor in the controversy over legislation that essentially prohibits the use of substances that have produced cancer in any test animals. That legislation, the Delaney clause of the Food, Drug, and Cosmetics Act, as amended in 1958, has led to the intense debate over saccharin, cyclamates, and other food additives which have had widespread use. Because of the lack of conclusive evidence whether demonstration of a substance causing cancer in animals means that the same substance will also cause cancer in humans, there is intense disagreement over whether the Delaney clause is a prudent protective measure or a bad case of over-regulation–particularly where the Delaney clause has been invoked to limit the use of some very widely used and commercially important products such as certain artificial sweeteners–and the issue remains one of controversy and significance.[47]

DOSE LEVELS [48]

Unlike epidemiological studies, laboratory researchers generally do have control over the application of the risk agent. However, there are frequently compelling experimental reasons for using doses which differ considerably from those which humans are likely to experience.

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[45] IRLG, p. 54

[46] IRLG Study, p. 15.

[47] Dodge, Christopher H. and Robert L. Civiak. Risk Assessment and Regulatory Policy, IB81019, archived Sept. 9, 1981.

[48] Except as noted, based on IRLG Study, p. 33-35.

In the first place, the smaller size of most test animals requires some scaling of the dose for strict comparability between the animal and humans. However, the scaling is not simply one of relative overall body weights. Differing metabolisms, respiration rates, organ uptake and elimination, etc., must be taken into account to achieve strict comparability. In instances where the mechanism of effect is not well understood, it may be difficiult to identify and quantify all the factors and therefore difficult to select strictly comparable dose levels.

Even if strictly comparable doses are known, it is often desirable to enhance or diminish the actual dose administered. Dose rates are most often enhanced in order to obtain sufficient data to complete the experiment in a reasonable period of time. That is, at low doses, the incidence of effect may be so small as to be unidentifiable in a limited sample size or time period. Higher doses can be selected with the belief that the effect scales with the dose. However, the results of such research in many cases might not be accurately indicative of the risks to humans who are generally exposed to much lower levels of a risk agent. For instance, the liver and other biological defense mechanisms which can detoxify or otherwise protect the body against limited doses of risk agents can be overwhelmed by very high concentrations of these same substances.[49] In the case of widely used consumer products, this has produced considerable controversy. The capabilities and limitations of this methodology will be explained further below.

On the other hand, sometimes doses are limited to less than the optimal experimental dose because of considerations related to administering the dose. This can occur if the agent, in the form administered, is toxic to the test animal in ways not of direct interest to the study, if the administration of the dose would prevent adequate uptake of required nutrients, if the desired dose level is rejected by the test animals because of alterations to taste of food, etc. In so far as judging comparability to human situations is concerned, this latter experimental limitation is probably of less concern than the former, although there may be some impacts on the experiment due to behavioral and perhaps other responses of the animal. The real concern is probably whether the experiment can obtain meaningful results with a reasonable test sample in a reasonable period of time.

METHOD OF ADMINISTRATION

Often doses of risk agents to experimental animals are administered in a different way than they are to humans. This is done for a variety of practical experimental reasons, including difficulty in administering sufficient doses in the same way as for humans, more accurate control of dose, or more ready monitoring of an impact. For example, if a substance under test is highly volatile, it may be difficult to administer it accurately in food because of evaporation; stomach tube feeding may be used in such cases so that the dose may be administered with greater control. A stomach tube may also be used for certain nonvolatile test substances when it is important to know or to control the exact amount of a substance administered. Finally, the administration of high doses of test substances with odors or tastes that cause the test animals to reject them may require the use of routes other than ingestion.

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[49] Thilly, William G. Chemicals, Genetic Damage and the Search for Truth, Technology Review, v. 83, Feb./Mar. 1981. p. 40.

The essential factor when using alternative routes of administration is that they be comparable in terms of evaluation of human hazard. For example, in some cases, the reaction of the skin of the animal to a risk agent may be similar to effects that could occur to the tissue of human organs; also, some chemicals are rapidly absorbed by inhalation, circulated through the body and metabolized by the same pathways that occur following intravenous exposure. In other cases, the method of administration is known to introduce different mechanisms for biological effect (such as causing a tumor response via physical mechanisms rather than chemical ones.) Therefore, for example, such things as "solid state" implants of test substances into connective tissues and chemicals administered jointly with particulate materials may yield results that are not indicative of the impact of the same substance administered in a different physical form.[50]

Because of such complex and not always completely understood questions of experimental comparability, the practice of using methods of application for laboratory tests that differ significantly from applicable human experience is still subject to considerable controversy, as for example, in the question of whether the occasional external application of hair dye equates to continuous, large doses of the same chemicals administered orally or injected internally.

Since the findings of risk agent studies seem to be specific to the risk agent, animal and method of administration, each case is different and requires careful consideration of physiological and metabolic similarities and differences related to routes of absorption and internal distribution in order to validate the comparability of alternative routes of administration.

RESEARCH PROTOCOLS

Research procedures may vary greatly from one experiment to another and therefore may introduce problems in the interpretation and use of data. For example, lifetime animal experiments are often difficult to interpret because of competing causes of death. Even if a specific condition, such as a tumor, is observed in pathological examinations subsequent to death, if the tumor is not the cause of death, the relationship between tumor incidence and mortality is difficult to determine. Furthermore, information from lifetime animal experments cannot appropriately be combined with data from experiments involving scheduled sacrifice, since the latter experimental animals are at a different stage of the life cycle. The most comprehensive experiments involve the use of serial sacrifices. However, such experiments require much larger test populations, and also impose other limitations on the research possibilities (in terms of researching the effects of the substance on survival or on causes of death).[51] Therefore, great care must be taken in examining, combining or comparing research results to assure that the data can appropriately be combined or compared, and to establish the meaningfulness of the data in providing information on the factor of interest.

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[50] IRLG Study, p. 29-31 and 54-55.

SAMPLE SIZE

Even though the researcher has a greater degree of control over the selection of a population than in the case of epidemiological studies, animal studies often are still limited because of the sample size of the study. As discussed in greater detail below, the small rate of incidence of certain impacts implies a need for large sample sizes for optimal statistical validity. However, animal research is often limited by funds, space, personnel, time, and test specimens.[52]

The limitations on sample size can be partially overcome by appropriate selection of dose levels, although that technique also has its limitations, as discussed in greater depth in chapter 5.

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[51] IRLG Study, p. 59.

[52] IRLG Study, p. 28.

CHAPTER 4: CELLULAR RESEARCH

INTRODUCTION [53]

Studies of the impacts of risk agents on biological specimens can also be conducted through in vitro, or laboratory, experiments using human, animal, or microorganism cell cultures. The major advantages of this type of research include the ability to examine very large numbers of test specimens and the ability to examine many "generations" of test specimens, all within much more modest cost, space and time constraints than are possible for laboratory experiments with animals. In fact, such tests are often called short-term carcinogen tests. Therefore, cellular tests can be very useful short-term or preliminary indicators of biological impact.

However, although single cells can in some sense model more complex organisms, such research does not completely represent all the conditions and interactions of a complex multicellular organism such as a human being. Consequently, most risk analyses do not rely on the results of cellular research alone. Nevertheless cellular studies can provide important suggestive evidence of an impact, valuable basic scientific understandings about risk agents and their mechanisms of biological impact, and complementary verification of other evidence. Furthermore, the Federal Government presently allows several in vitro tests to substitute for preliminary animal cancer screens in certain cases, such as for drugs administered to food animals.[54]

Cellular research, as applied to risk agents, is basically concerned with the manifestations of a risk agent at the level of the single cell. The two major classes of cellular research are therefore research methods based on genetic alterations (including chromosomal changes) and research methods based on neoplastic cell transformations (i.e., the growth of different or abnormal tissue, such as a tumor).[55]

The major types of genetic tests involve examinations of single cells, or colonies of cells, and include:

Tests for mutations in bacteria and certain microorganisms;
Tests for mutations in somatic mammalian cells;
Tests on chromosomal effects in certain microorganisms and cells; and
Evaluation of DNA repair synthesis.

Microorganisms widely used for mutagenicity tests include: Salmonella, E. coli, Saccharomyces, Neurospora, and Aspergillus. Drosophila (fruit flies) are also used for mutagenicity testing, and are generally considered in the class of cellular tests. A sampling of known mutagens and the results of different cellular tests used to study them are shown in Table 9. It is particularly interesting to observe the apparent disparity of results between tests done on different organisms, thus illustrating graphically the inconclusiveness of a single test, and the need for careful research design and analysis.

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[53] Based on IRLG Study, except where indicated.

[54] Holden, Constance. New Focus on Replacing Animals in the Lab. Science, v. 215, Jan. 1, 1982. p. 35-8.

[55] Other types of cell transformations may be of interest in the case of some risk agents (i.e., hyperplasia in the case of formaldehyde), but neoplastic cell transformations are of the greatest concern and have received the greatest research attention.

TABLE 9. SOME EFFECTIVE MUTAGENS STUDIES IN DIFFERENT ORGANISMS * [a]

Mutagen	Drosophila	Neurospora reversions	Higher plants	Bacteria	Source of exposure
Mustard derivatives: Nitrogen mustards	+	+	+	+	Therapy.
Epoxides: + +					
Epoxide	+	+	+	+	Industry.
Diepoxybutane					Domestic Use.
Imines: Triethylenemelamine (TEM)	+	+	+	+	Therapy.
Alkane-sulfonic esters:	+	+	+	+	Therapy.
Dimethylsulfonoxybutane					
(Myleran)					
Other alkylating agents:	+	+	+	+	
Dimethyl sulfate					
Diethyl sulfate					
Peroxides: + +					Smog.
Tert, butyl hydroperoxide	+	+	}	}	
Dihydroxymethyl peroxide	+	+	}	}	
Aldehydes: + +	+	+	{	+	
Formaldehyde					Industry.
Propionaldehyde					Smog.
Acrolein					Disinfectant.
Basic dyes: + +					Industry.
Proflavine, Pyronine, Acridine orange	+	}	}	+	
Purines: + +					
Caffeine	{	}	}	+	Beverages.
8-ethoxy caffeine	**	}	Chroms #	}	Widespread use.
Antimetabolites: + +					
5-bromouracil 2-aminopurine	**	}	}	+	Therapy.
Pyrrolizidine alkaloids	+	}	}	}	Herbs.
Miscellaneous:					
Nitrous acid	}	}	}	+	
Phenol	+	**	Chroms #	}	Industry.
Manganous chloride	**	}	}	+	
Urethane	+	**	Chroms #	}	
Diazomethane	+	+	}	}	
Beta-propiolactone	}	+	+	+	
Maleic hydrazide + +	**	**	Chroms #	**	Food, agriculture.
Ethyl alcohol + +	**	**	Chroms #	**	Widespread.
Nicotine + +	**	**	Chroms #	**	Widespread.

[a] Brannigan, Francis. The Potential Hazard from Radiation. Nuclear Safety, v. 5, Spring 1964. p. 226-228.
* One or more typical examples in each class of mutagen.
+ Mutagenic.
+ + Of common occurrence, at least in certain human environments.
} No reference to mutagenic activity available.
{ Weakly mutagenic.
** Not mutagenic.
# Produces chromosome breaks in plants.

Tests for neoplastic cell transformations differ from mutagenicity tests in that they involve examinations of cell colonies for the frequency of morphologic alterations. Such tests can be done with embryo cells or a variety of specialized cell types. The cell tissues most widely used are golden hamster embryo cell systems and mouse embryo fibroblast cell line systems. Other tissues that have been used include human white blood cells,[56] and epithelial cells from the liver, epidermis and other organs. Findings of changes in the cultured cells are sometimes further tested in animals by examining animals inoculated with the transformed colonies under certain controlled conditions (in addition to performing studies on animals by applying the risk agent directly to them).

RANGE OF VALIDITY

Cellular research is essentially limited to the examination of risks which have direct impacts at the cellular level. This includes some very important classes of risks, primarily the whole spectrum of cancer risks, which is a class of risks of concern for a large number of food and environmental risk agents. However, it does not provide direct information about diseases or conditions which do not, to present knowledge, alter or otherwise impair individual cells. Thus cellular research is not effective, at present, in providing information about some important classes of risk agent related diseases such as pulmonary or respiratory ailments.

BIOLOGICAL INTERACTIONS

For a variety of reasons, laboratory tests of the impacts of a particular risk agent on a single cell are not always accurate indicators of impact on a complex multicellular organism. The discrepancy may operate in both directions--that is, there may be risk agents which have an effect on a higher organism that is not reflected at the single cell level, or there may be risk agents which have no apparent effect on higher organisms, but which show evidence of morphologic transformations in cellular cultures. Therefore, short-term tests alone, in the absence of other evidence, are generally not considered to constitute definitive evidence as to whether a substance does or does not pose a hazard to humans.

Enzymatic Interactions

Certain chemical risks agents require, for their effect, metabolic activation by cellular enzymes. Cells in culture may retain their enzymatic activities, but some culture systems or preparations may lack, or may lose, the critical enzymatic activity. Reserpine and cinnamyl anthranilate, for example, are two compounds that have been found to affect enzymatic activities and carcinogenisis in higher organisms (e.g., rats, and mice), but do not affect cell culture tests.[57] Therefore, a negative finding of effect in a cell culture test is not, in the absence of corroborating animal bioassay or epidemiologic data, necessarily indicative of the safety of the agent for multicellular organisms. For carcinogens specifically, according to the NCAB subcommittee on environmental carcinogens:

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[56] Thilly, William G. Chemicals, Genetic Damage and the Search for Truth. Technology Review, v. 83, Feb./Mar. 1981. p. 39.

[57] Molecular and Cellular Aspects of Carcinogenic Screening Tests, Montesanto, R., H. Bartsch, and L. Tomatis, eds. Mutagenic Activity of Chemicals Previously Tested for Carcinogenicity in the National Cancer Institute Bioassay Program. Dunkel, V. C. and V. F. Simmon. IARC Science Publication #27 (1980).

At the present, none of the short-term tests can be used to establish whether a compound will or will not be carcinogenic in humans or experimental animals. Positive results obtained in these systems suggest extensive testing of the agent in the long-term animal bioassays, particularly if there are other reasons for testing. Negative results in a short-term test, however, do not establish the safety of the agent.[58]

Multicellular Mechanisms

It may be difficult to identify absolutely what biological mechanisms may cause a substance to produce a positive response in cellular tests but an apparently negative one in animal tests. The concern, from the viewpoint of technical rigor, is that an apparent negative result in animal tests may really reflect a lack of observability of the effect rather than a lack of effect altogether; that is, an effect may really exist, but the test isn't sensitive enough to discern it. However, there may also be certain biological processes in multicellular organisms that can partially or completely counteract effects on single cells. Such processes may include the ability of multicellular organisms to compensate for certain impaired functions and/or to defend themselves against certain invasive agents. Thus, while a positive response in a single cell test is strong evidence of the potential for impact at the multicellular level, such evidence may sometimes be countered by thorough testing of higher organisms and epidemiological research that completely fails to corroborate the findings of the cellular research.

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[58] General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances. Journal of the National Cancer Institute, v. 58, 1977, p. 461-465, and Addendum 58, 1977, p. 1544.

CHAPTER 5: DOSE EXTRAPOLATION

INTRODUCTION

Risk agent studies commonly use techniques which determine the impact of the agent at a particular dose by extrapolating from data available at other doses. This technique is often required because, for a variety of reasons, data may not be available at dose levels of interest. In the case of epidemiological studies, dose administration is not controlled by the researcher and historical exposures may not be at the doses of primary interest. For example, data from industrial radiation accidents or atomic bomb exposures is extrapolated to determine the impact of low-level radiation doses.[59] In the case of experimental research on animals, doses may be administered at much higher levels than are generally of practical interest for reasons of experimental feasibility–in other words, to allow the accumulation of data in a reasonable amount of time, to allow for the collection of sufficient data to assure statistical validity (see previous section), etc.

Extrapolations from existing data are performed in several ways. One method involves simply extending the shape of the curve formed by a graphical display of the existing data. Another method extrapolates the shape of the curve based upon theoretical arguments as to biological and physical mechanisms operating. Still another option is to utilize fragmentary or statistically uncertain experimental data points which may be available in the region in question. In some cases, extrapolations performed using the different methods may disagree, or, in the case of extrapolations based on theoretical arguments or on isolated data points, there may be several curves that can be postulated, depending on the data selected or the theory chosen. For example, in the case of radiation, there is significant controversy at present over which method of dose extrapolation is appropriate in low dose regions; experimental and/or theoretical arguments can support any of several dose extrapolation methods.[60]

Figure 3 illustrates schematically the major dose extrapolation arguments for radiation exposure. Similar curves can be postulated for many other risk agents. Curve a is often called the linear model; curve b is called the threshold model; curve c represents a model in which the effects at low doses are disproportionately lower than those for higher doses (the quadratic or dose-squared, and linear-quadratic models are examples); and curve d represents the opposite case, in which the effects at low doses are disproportionately higher than those at higher doses. Each of these is discussed briefly below.

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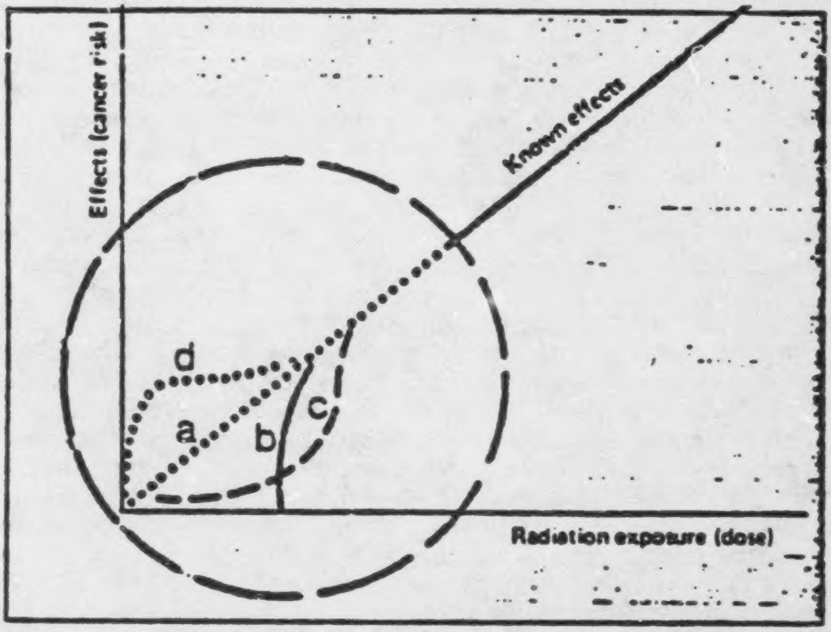
[59] It is interesting to note, however, that ionizing radiation is, by a significant margin, the most extensively studied human risk agent. It is the only risk agent for which substantial human dose response data has been established at relatively low levels of exposure, and yet, even in this case, not even a scientific consensus yet exists, let alone a social or political one. This scientific disagreement is perhaps epitomized by the National Academy of Sciences report, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980 (known as BEIR-III), which includes dissenting statements prepared by members of the Committee on Biological Effects of Ionizing Radiation which wrote the report, because of "unresolvable differences" between members of the Committee.

[60] See, for example: Edward P. Radford, Cancer Risks from Ionizing Radiation, Technology Review, v. 84, Nov.-Dec. 1981, p. 66-78.

Two qualifying explanations should be mentioned. First, for most risk effects, there is some natural incidence of the disease or effect, even in the absence of the risk agent. Normally, when dose-effect considerations are discussed, the curves used are adjusted to reflect only the effect over and above the natural "background" level of the effect by subtracting from the test data the incidence of the effect for a control sample not exposed to the risk agent. The curves shown throughout this section reflect such an adjustment.

Figure 3.—Some Proposed Models of How the Effects of Radiation Vary With Doses at Low Levels[a]



Secondly, the text discusses mainly "pure" models. In reality, dose effects may, of course, reflect some combination of phenomena, and therefore have a shape somewhere between two of the pure cases. The linear-quadratic curve described below is a manifestation of two physical phenomena operating simultaneously.

Linear Dose-Effect Theory

Linear dose-effect theory (curve a) says in essence that the effect of the risk agent is zero at zero dose level and increases in exact proportion to the increase in dose. This proportionality suggests that, if some dose-effect relationships have been measured at high

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doses, one simply needs to draw a straight line on a graph between these measured points and the zero point on the graph in order to determine the effect of any lower dose. Strictly interpreted, this theory implies that there is no dose so small that it has no effect at all–even if the effect is too small to be measured, if there is some dose, there is some impact. The theory may be conservative for substances for which repair mechanisms or other ameliorating processes operate at small enough doses. It is therefore often used to indicate an upper bound to the risks at low doses. This theory was initially developed as a model for radiation exposure impacts. Similar relationships may occur for other risk agents, but because the physical and chemical processes involved are likely to be very different, any attempt to apply the same concept in different cases is usually regarded with extreme caution.[61]

THRESHOLD THEORY

Threshold theory (curve b) provides a different description of dose-effect behavior at low doses. According to this theory, for certain substances there is a dose below which no damaging effect of the risk agent occurs, either because the substance simply has no biological impact in that dose region, because a risk agent in small enough quantities can be chemically neutralized, or because the body can heal itself from small enough insults. According to this theory, biological impacts start at some threshold dose level, and then increase as in other theories (usually linearly). Because of the limitations in measuring effects at small doses, it is often difficult to distinguish between cases where no effect is observable and where no effect actually occurs. Therefore, there are conflicting opinions about whether this theory is valid for particular substances, such as radiation. If this theory is correct for radiation, it would provide assurance that most dose levels of radiation to the public expected from reactors under normal operating conditions and for many classes of accidents are harmless; if it is not correct, the use of this theory could tend to underestimate the hazard at low dose levels. However, at present, for radiation:

> Very few radiobiologists still cling to this hypothesis: The consensus of scientific opinion is that even very small doses of radiation may give rise to a very small but finite increase in the incidence of cancer; but there is a considerable difference of opinion about the magnitude of that increase, especially about the way it varies with the dose, for different types of radiation.[62]

For chemicals risk agents, on the other hand, a threshold mechanism may be postulated based on the normal concentrations of metabolic products and chemical repair mechanisms. Pochin has noted that, for carcinogenic products:

> for many chemical pollutants, the metabolic products which are carcinogenic may have zero tissue concentrations under 'normal' circumstances. This would, if so, differ from radiation increments to natural radiation exposure and imply that chemical repair mechanisms might be more likely to impose a 'threshold' below which no effects occur.[63]

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[61] Dealing with Risk, Ed. Richard F. Griffiths, Halsted Press, Great Britain, 1981. p. xvii; and E.E. Pochin. Assumptions of Linearity in DoseEffect Relationships. Environmental Health Perspectives, v. 22, p. 103-5 (1978).

[62] Rotblat, ibid., p. 32.

[63] Pochin, ibid.

QUADRATIC MODELS

One type of dose relationship which has received considerable attention recently is described mathematically by the following formula:

$$I=(Io + aD + bD2)e - (eD + bD2)$$

where I is the disease incidence after exposure to a dose D, and I_0 is the natural incidence of the given type of disease.[64] The model has been discussed primarily for the case of cancer incidence due to radiation exposure, so the remainder of the discussion is with reference to that situation, although elements of this model may apply to other risk agents.

Ignoring the exponential term, which becomes significant only at higher doses, the formula shows that at low doses the increase in cancer cases is the sum of two terms--the first giving an increase linearly proportional to the dose, and the second an increase proportional to the square of the dose. Depending on the values of the parameters a and b, three models can be distinguished:

> the linear model (discussed above), which applies when b is so small that bD^2can be neglected compared with aD over the relevant range of doses;
>
> the quadratic model, if the first term can be neglected;
>
> the linear-quadratic model, if both terms contribute significantly.

Figure 4 shows sample dose-response curves of increased cancer incidence $(I - I_0)$ for the three models at low dose levels. At the very low doses of concern from the point of view of population exposures to radiation, the difference between the linear and quadratic models may be as much as a factor of 100. Therefore, the type of model adopted can be important in the extrapolation from known data at high doses.[65]

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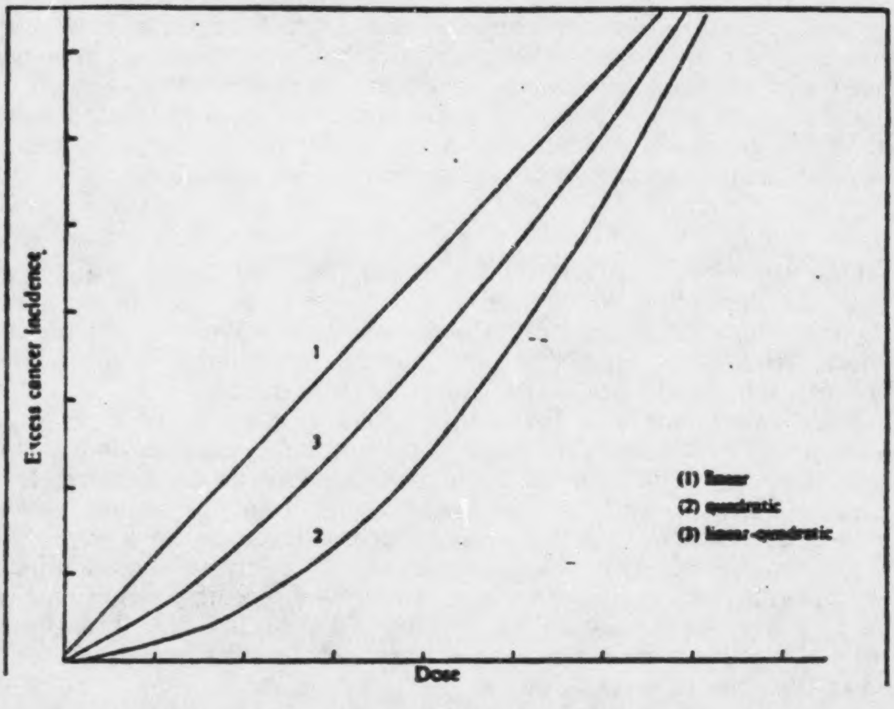
[64] Rotblat, ibid., p. 33.

[65] Rotblat, ibid., p. 33.

FIGURE 4.—INCREASED CANCER INCIDENCE AS A FUNCTION OF DOSE FOR LOW RADIATION DOSES, ACCORDING TO THREE MODELS [a]



For radiation, the theory behind these curves is based upon the assumption–derived from comparisons of the biological effects of different radiations with their energy transfer characteristics–that the induction of cancer is a "multihit" process (that is, a process requiring several electrons in a molecule to be knocked out of position). Curves of different shapes result depending upon whether the multiple hits (a two hit process is generally assumed) are from the same particle of radiation or from different particles of radiation. The former results in an effect that is proportional to dose; the latter results in an effect that is proportional to the square of the dose. The magnitude of the coefficients a and b depend both on the type of radiation and its energy.[66]

LOW DOSE ENHANCEMENT THEORIES

Curve d, showing a disproportionately high impact from low doses, is based primarily on interpretations of certain experimental evidence. However, in general, this experimental evidence is considered unreliable by the majority of scientists in the field. In the case of radiation, for example, the adherents of this curve base their evidence on studies of population subgroups believed to be

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[a] Rotblat, Joseph. Hazards of Low-Level Radiation–Less Agreement, More Confusion. Bulletin of the Atomic Scientists, v. 37, June/July 1981. p. 32.

[66] Cohen, Bernard L. The Cancer Risk from Low-Level Radiation. Health Physics, v. 39, Oct. 1980. p. 659-678.

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particularly susceptible to a risk agent. These studies have been challenged by other scientists, who have reexamined the data and found no correlation between the alleged indicators of susceptibility (allergies and infectious diseases) and the incidence of leukemia among radiation-exposed subjects and control subjects in a retrospective epidemiological study.[67] (Low dose enhancement theory is not based on the same phenomenon as the exponential term of the equation previously discussed because the impacts of that phenomenon are generally operative at a larger doses. The large dose exponential phenomenon wili be discussed in a later section.)

HORMESIS

One theory which should be mentioned briefly in conjunction with the dose-effect discussion is a concept known as hormesis--the theory that a risk agent may have beneficial effects at low enough doses. This theory involves some complex and highly controversial notions, which will not be examined here in depth.

It is important to note that the benefit may be of a different nature than the risk. This dual nature of some substances has long been known to be true of certain drugs and foods--ranging from curare, quinine, and aspirin to vitamins--many of which have a beneficial impact at small enough doses, but can be harmful, or even lethal, at larger doses. Recent highly controversial studies of radiation effects are also beginning to reveal possible beneficial impacts, such as increased lifespans, at low dose levels,[68] but the results to date are fragmentary and are not currently widely accepted in the scientific community.

LARGE DOSE EFFECTS

Although most of the methodological concerns about dose effects involve low doses, a few comments about the effects of large doses are in order. As the dose of a risk agent increases, the dose-effect curve in some cases can level off or even decrease, depending on the risk agent and the effect. Mathematically, such an effect is represented by the exponential term of the formula discussed above. A schematic curve over a large dose range that includes the effect of the exponential term is shown in Figure 5.

In fact, by itself, this term indicates a decrease in disease incidence as the dose is increased. This seemingly paradoxical effect can be explained by examining the physical mechanisms that are operative. One effect that tends to yield a saturation of damage is that incremental amounts of a risk agent often cannot further damage tissue already damaged by the risk agent. In addition, for the case of radiation, the risk agent can both convert normal cells into cancerous cells, and can also kill all types of cells. At high doses most of the cells which would otherwise become cancerous are killed, resulting in a proportional reduction in cancer incidence. The downward exponential trend of the curve in figure 5 tends to compensate the increasing upward trend due to the quadratic term in the formula; therefore, the dose-response curve appears to be linear over a large range of doses--even with the linear-quadratic model (as can be seen in Figure 5).[69]

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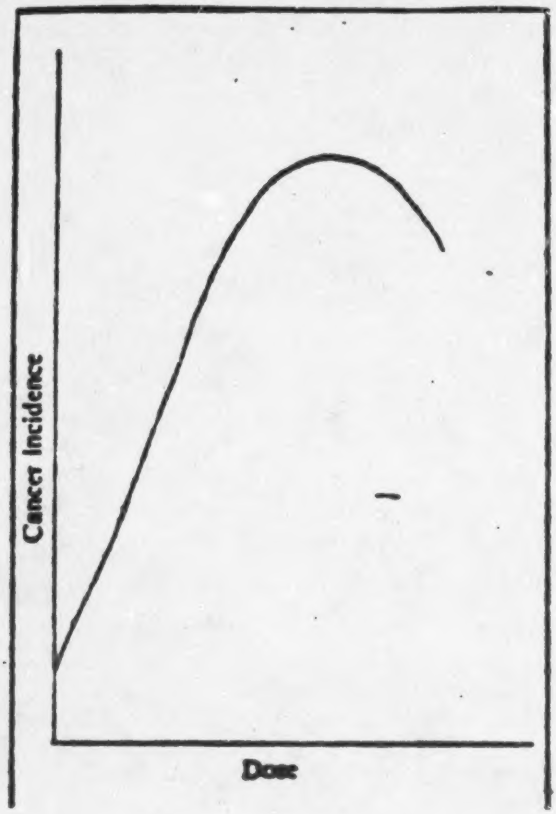
[67] IAEA, p. 13.

[68] Luckey, T. D. Hormesis with Ionizing Radiation: Health Physics Journal, v. 25, 1972; McGregor, John F., and Howard B. Newcomb. Radiation Research. Dec. 1972.

FIGURE 5.—THEORETICAL VARIATION OF CANCER INCIDENCE WITH DOSE.[a]



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[69] Ibid., p. 33-34.
[a] Rotblat, Hazards of Low-level Radiation, p. 33.

CHAPTER 6: SAMPLE SIZE

INTRODUCTION

The problems resulting from inadequate experimental populations, or sample sizes, have been mentioned several times, in connection with both epidemiological studies and animal research. Since this problem is common to both types of research, the basic considerations outlined here apply to both. It is not the purpose of this section to present detailed mathematical analyses of statistical validity. Rather, the correlations between sample size and statistical validity will be discussed in a general fashion.

There are several major elements that affect the sample size required to produce statistically meaningful results. These include the very low incidences of effects from some risk agents, the statistical variability possible in examining the incidence of any effect in any sample group, the degree of confidence in the results required, and the natural incidence in the target population of many of the same diseases or health effects that are produced by risk agents. Each of these considerations will be examined in turn.

LOW INCIDENCE

At the low doses of usual exposures, many risk agents induce a rather small number of effects in human and other animal populations. Of course, a low incidence of effects means, from a practical standpoint, that the substance is relatively safe. However, from an experimental standpoint, the exact dimensions of the risk become more difficult to determine. For example, if impacts are in the range of a few effects per hundred thousand people, any tests conducted on a much smaller sample size, say a few hundred people, can well fail to indicate any level of impact. That is one reason that many potentially hazardous substances have entered the public domain. Limited tests failed to reveal a problem, and scientific knowledge was inadequate to predict that there might be a problem. However, when very large fractions of the population--millions of people--began to be exposed, the effects of the agent became more evident.

The whole difficulty of dealing with small sample sizes does not, of course, arise in cases where the risk agent is extremely virulent, as in the case of many highly toxic chemical poisons. In those cases, a small sample size will quite clearly and adequately reveal the cause-effect relationship. On the other hand, if there are any substances which induce a risk in the human population at a level of one case in a billion, any effect will probably occur too few times to be correlated with the cause. In fact, the chances are good that the effect might never occur, even if the entire current world population were exposed.

There are several reasons why a low incidence of an effect from a risk agent can occur. A primary one is probably differences in individual resistance. For reasons we do not entirely understand at present, individuals seem to have significantly different abilities to combat various diseases or physical injury, depending on race, sex, age, genetic disposition, synergistic effects of exposure to other chemicals, or other factors.[70] Thus, a small cancer risk might primarily reflect the fact that a small proportion of the population is far more susceptible to cancer-causing risks than is the general population. Our present state of scientific knowledge, however, is such that we have no way of identifying these people, predicting who they will be, isolating the cause of their susceptibility (or, conversely, of the resistance of the rest of the population), or altering their susceptibility.

Another possible cause of different effects in different individuals, at least for certain exposures to certain risk agents, is that the fact of exposure does not mean that the risk agent had the opportunity to interact identically with each organism. In effect, in many cases, given an exposure to a risk agent, there is only a probability that it will interact with the exposed organism in such a way as to produce an effect–radiation, for example, might have to hit a certain number of cells within a given volume of tissue to create irreparable damage leading ultimately to cancer, and for sufficiently low doses, there might be only a limited probability of that happening.

From a research viewpoint, one practical consequence of low incidences of effects is that, the lower the risk agent dose, the lower the effect, and therefore, the larger the population that must be observed to measure the consequences of exposure reliably. For example,

> As the radiation dose becomes smaller, its effects become fewer. So, to demonstrate conclusively that certain health effects are associated with a given radiation dose, the number of people that must be observed becomes larger and larger as the radiation dose decreases. (For example, to detect any change in the number of genetic defects that could be caused by an increase in radiation dose of 3 millirem per person per year, one would need to observe a population of 700 million people for three generations). [71]

Furthermore, the problems of low incidence may be exacerbated in cases where not all the exposed population is susceptible, or equally susceptible, to the effect, thus making the effective sample size even smaller than the population exposed. This can be the case, for example, for sex-linked effects (such as prostrate cancer for men, breast cancer for women), or for synergistic effects (such as smoking and asbestos exposure).

STATISTICAL VARIABILITY

Another factor that influences the sample size required for risk agent experiments and studies is the phenomenon of statistical variability. This is the same phenomenon that operates when a coin or a pair of dice is tossed. Most people are familiar with the fact that, although probabilistically half of a given number of coin tosses should be "heads," in fact, when the total number of tosses is small, the mix of heads and tails can deviate from 50-50 considerably. For example, in four tosses, it would not be extremely unusual to obtain all heads, or all tails. In fact, the probability for each of those two cases is 1/2x1/2x1/2x1/2, or a little over six percent. On the other hand, in 100 coin tosses, it would be much more improbable to obtain 100 consecutive heads or tails (the probability in this case is $(1/2)^{100}$, or about 10^{-30}; the mix of heads and tails can still deviate from 50-50, but not by such a large percentage as with a small number of tosses).

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[70] Calkins, D.R., et.al., Identification, Characterization, and Control of Potential Human Carcinogens: A Framework for Federal Decisionmaking, JCNI, v. 64, Jan. 1980, p. 169-176; Science and the Citizen: Predispositions, Scientific American, v. 243, Aug. 1980, p. 80-82A.

[71] IAEA, p. 11.

Although the effect of a risk agent may be far more complex than a heads or tails phenomenon (for example, there may be more than two possible outcomes or effects) the probabilistic consequences of small numbers still apply. That is, in an examination of a very small sample group, there is a reasonable chance that the outcome will deviate considerably from the outcome that a larger sample size might have.

This effect is obviously exacerbated in cases where the phenomenon under investigation has a low incidence in the first place. In the case of the coin, the incidence of the desired event (in this case, heads) is 50 percent. Therefore, although an anomalous outcome might occur from a test of, say, four coin tosses, it does not take too many tosses to reach a state where the effect of sample size has clearly been reduced to reasonable proportions for experimental purposes. Certainly, a 100 toss test sample should be expected to provide results that realistically reflect what can be expected from larger sample sizes.

However, in cases where the incidence of the effect is only a few in a 100,000, a sample size of a 100,000 is really a very small sample size for statistical purposes. That is, if "a few" is 5 in 100,000, on the average, in any given group of 100,000, there might be an actual incidence of three cases or eight cases, but one could not attribute such a difference, on the basis of that evidence alone, to being due to a difference in exposure or in the population group. Given identical exposures, apparently identical population groups of 100,000 might reasonably be expected to have three or five or eight cases of the effect.

Confidence Levels

Because of the statistical variability of many scientific results, scientists often speak of probabilistic outcomes in terms of "confidence levels." These are numerical expressions of the degree of certainty that the result is not an anomaly, that the sample size is large enough to assure that the result will be reliable. A confidence level of 50 percent, for example, indicates that there is only a 50-50 chance that the result is correct; there is an equal chance that the result could be incorrect. Scientists generally like to express their results at the 95 percent confidence level–this represents a high degree of certainty that the result is accurate and reproducible.

Such differences are often expressed in terms of a confidence level that the results are within a certain range, or interval, of a particular value. For example, in the case discussed above, there might be a 50 percent confidence level that the effect has an incidence of three to eight effects per 100,000 people, but a 95 percent confidence level that the effect has an incidence of 0 - 12 effects per 100,000 people. In other words, the larger the interval, the more likely that observed results will fall within that interval. However, the latter interval means that the possibility that there is no measurable effect at all cannot be excluded. Differences in confidence levels used can be one reason why different experts will disagree on the interpretation and significance of a particular finding.

NATURAL INCIDENCE

For many, if not most, risk agents the effects they cause also exist in the human population to some extent or another in the absence of the risk agent, either as a "natural" phenomenon, or as a consequence of exposure to something else, or for unknown reasons. This is true, as far as we know, of most of the major risk effects studied, such as cancers, birth defects, and respiratory illnesses, as well as of many other types of diseases. This natural level compounds the difficulty of measuring levels of disease incidence attributable to the particular risk agent, because the measurement must be made against the background "noise", so to speak, of the natural occurrence.

The noise factor refers to the statistical variability of naturally occuring disease effects, the same statistical variability that was previously discussed in terms of risk agents. For example, identical populations of 100,000 people exposed to a common natural environment containing no known risk agents might have incidences of a given disease, such as leukemia, that varied over some range, such as discussed above. Therefore, if the nominal incidence of a disease from natural causes in the absence of the risk agent is 5 per 100,000, an incidence of 7 disease cases in a sample of 100,000 people exposed to a risk agent would not be conclusive--it would be impossible to determine if the extra two cases were due to the risk agent or due simply to the statistical variability in outcomes.

Clearly, the difficulty that the natural disease incidence poses from a research point of view varies considerably with the relative sizes of the natural and risk agent induced incidences. If the natural occurrence is very small and the risk agent induces effects at a much higher level, the risk agent induced effects overwhelm the natural incidence, and a cause and effect case can be established much more readily and reliably than would otherwise be the case. This was the case with thalidomide, where the natural occurrence of the effect was very rare, and the risk agent induced effects at much higher levels. However, if the risk agent induces only a small number of effects compared to the natural incidence of the same effect, it is impossible to ascertain that the risk agent actually had any effect. This is the case, for example, with the radiation exposure from the Three Mile Island incident, where the expected increase in fatal cancer is only one or two, which will be undiscernable against the background incidence of cancer in that population.[72]

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[72] President's Commission on the Accident at Three Mile Island report--The Need for Change. Washington, U.S. Govt. Print. Off., 1979, 201 p. (Kemeny Commission Report).

Naturally, in the extreme, for the case of an effect from a risk agent which has no natural incidence, the experimental situation becomes much simpler. The incidence of even one case of the effect, if it can be reliably traced to exposure to the risk agent, is fairly conclusive of a cause-effect relationship (barring of course the very improbable case of an almost one of a kind event from some other, supposedly benign or well understood, element of the test subject's background environment). Of course, a test sample size of one individual would not be sufficient to establish the probability of incidence of an event in a larger population, as discussed earlier; statistically adequate sample sizes would still be required for that purpose.

CHAPTER 7: MODELS

INTRODUCTION

Models of biological, chemical, and physical processes have a very important use in risk assessment and evaluation. They are often a vital adjunct to experimental and epidemiological data in establishing the nature and magnitude of an effect, determining causative mechanisms for the effect, predicting the consequences of changes in exposure to the risk agent, exploring the effects of palliative measures, charting the expected development and progress of long term effects, and performing a variety of other tasks that cannot be accomplished on a real time or in a real life basis.

Several different types of models can be used in conjunction with risk assessments, including biological, environmental, ecological, mechanical, and other models. The particular models used in a given case depend on the specific aspects of the environment, the ecology, the man-made systems, and the biological systems involved.

It would not be possible, in a report such as this, to document every model used in risk assessment. This chapter, therefore, briefly describes each of the major types of model, and discusses a few of the major characteristics that affect the accuracy and reliability of all models, namely, technical knowledge, comprehensiveness and complexity. The following chapter discusses separately one type of model which has achieved considerable importance in risk analysis recently–probabilistic risk assessment.

TYPES OF MODELS

One way of categorizing the multiplicity of models that can be applied in risk assessments is to characterize them as either biological, environmental, ecological, mechanical, or other. While these designations are primarily a matter of convenience, they can be helpful in understanding some of the points in an analysis of a risk at which models can usefully be applied.

Biological

Looking first at biological models, this category includes models of the biological processes of an organism, both at the microscopic and macroscopic levels, including processes that control uptake and residence time of natural or man-made foreign substances; mechanisms of cellular or organ damage or dysfunction; mechanisms of repair, etc.

Some specific examples of models that might be used in a risk assessment include: models of the transport of substances in the human cardiovascular system; models of the human respiratory system relating inhaled particulates of certain sizes to pulmonary or bronchial diseases; models of the alimentary system, to establish residence times of various substances in the body based on intake and elimination rates; models of the transport of individual chemicals through the body to determine residence time and site of activity, as for radioactive strontium 90 in bones; models of single cell reproduction processes and the effects of various chemicals or other risk agents in damaging the reproductive materials of cells or interfering with reproductive processes; as well as many others.

Environmental [73]

Environmental models refer specifically to models of the land, air, and water, independent of the existence of, or influence of, living plants or animals. Such models can encompass a very limited geographical segment, such as a model of an atmospheric layer a few kilometers deep, or a very large geographical extent, such as for global weather patterns, and can range over short or very long time periods. These models include models of the flows of air and water; the composition of air, water, or soils; the transport of materials in air, water, and land; climatic factors and elements that can effect them; altitude related factors; etc.

Samples of environmental models that might play a role in a risk assessment include: models of the creation and destruction of ozone in the upper atmosphere; models of the effects of carbon dioxide on long-term climatic conditions, models of the chemistry, transport and deposition of acid rain; models of the photochemical processes associated with smog; models of the circulation of ocean currents in distributing hazardous materials disposed of at sea; models of wind directions and velocities and precipitation patterns that might effect the transport of pollutants from normal or accidental industrial or power plant emissions; models comparing the effects of natural and manmade occurrences on weather patterns or pollution hazards, such as models of the composition and distribution of volcanic matter, etc.

Ecological [74]

Ecological models specifically cover the interactions of living organisms with their environment and/or with each other. An ecological model may be limited to a very specific and limited locale, such as a single lake, or can cover large portions of the globe. Ecological models include models of the life cycles of various animal and plant forms residing in a given area; the resources each requires; predatory relationships; migratory patterns; biological competition; etc.

Some samples of ecological models that can be applied to the analysis of risk agents include: models of the concentration and migration of mercury in the food chain (for example for swordfish); models of the life cycles of particular endangered species and the impact of man-made activities on them; models of the life cycles of "pests" that transmit diseases or effect food supplies to discover natural predators or vulnerable points in the life cycle; etc.

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[73] Environmental and ecological models have a large degree of commonality and are therefore often grouped together for purposes of discussion.

[74] Ibid.

Mechanical

Mechanical models are models of various complex man-made systems whose routine or abnormal performance could pose a risk to human populations. Specifically, mechanical models include models of the performance of man-made systems; structural integrity against various assaults; failure mechanisms and rates; performance of backup systems; etc. Probably the most well-known example of a model of a mechanical system is the probabilistic model of nuclear power plant accidents, which will be discussed in greater detail in the following chapter. Probabilistic analysis is, or can be, extended to many other critical man-made systems as well, and in fact, at least in special cases, analyses have been done of dam failures; accident probabilities in the transportation of hazardous materials; aircraft accidents in populated areas, and a host of other possibilities.

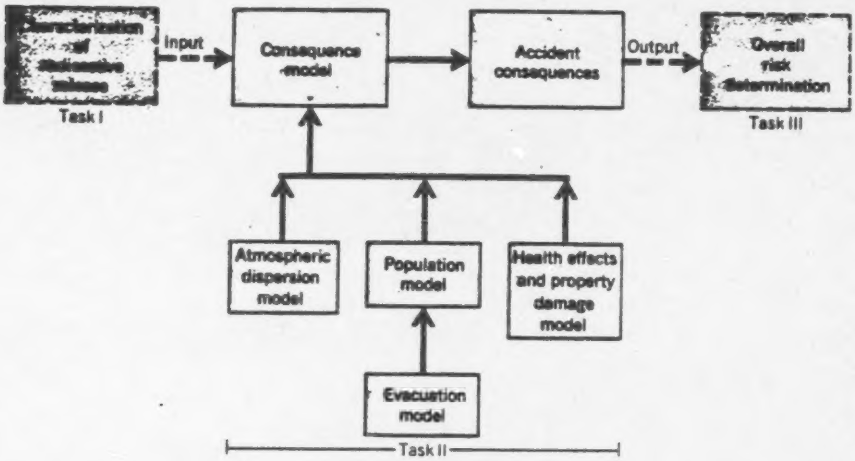
Other

Demographic models involve models of populations, population densities, population movements, and population characteristics. Some examples of population models useful for risk assessments include: population distribution within a geographical area surrounding a man-made or natural source of potential risk (including dams, powerplants, volcanoes, aircraft flight paths, etc.); models of the age distribution of a given population, in order to estimate the expected incidence of long-term risk effects; and models of mobility patterns of human population groups to estimate exposure to risk, populations available for epidemiological studies; etc.

Some models used in risk analysis are, effectively, composite models, and may draw on elements of several of the above types of models. These include such models as evacuation models, which take into account population factors, the local and regional highway structure, volunteer organizations, the existence and nature of plans and agreements relating to an evacuation, and weather models to determine the likely influence of weather on evacuation success.

Figure 6 shows how some of these models might play a role in a major risk assessment, such as one for a nuclear power plant accident. In a given case, the consequences of a radioactive release depend upon how radioactivity is dispersed in the environment (i.e., weather factors), the number of people and amount of property exposed, and the effects of radiation exposure on people and contamination of property. The figure indicates schematically the principal subtasks involved in analyzing these factors in the reactor safety study and how they contribute to the final results.

FIGURE 6.—SCHEMATIC ILLUSTRATION OF ROLE OF VARIOUS MODELS IN A MAJOR RISK ASSESSMENT STUDY [a]


Characterization of radioactive release
Task I
Input
Consequence model
Accident consequences
Output
Overall risk determination
Task III
Atmospheric dispersion model
Population model
Health effects and property damage model
Evacuation model
Task II

ACCURACY OF TECHNICAL KNOWLEDGE

Any model is only as good as the information upon which it is based. The information used to develop a model can be based on experimental data, theoretical concepts, or a combination of both. Some of the possible shortcomings of experimental data have been discussed in chapters 3 and 4 will not be repeated here.

Theoretical data, in some cases, can be subject to similar shortcomings. Some of the concerns about the use of theoretical data include: the correctness of extrapolating theoretical knowledge to new areas (for example, before Einstein's discoveries, a model examining objects moving at very high velocities would not have incorporated the formulas developed by Einstein relating velocity and mass and postulating a velocity limit of the speed of light); the completeness of theoretical knowledge (does it accurately cover all phenomena?); the accuracy of the theory (as knowledge is developed, refinements are sometimes added to previous theories that result in slight--or occasionally considerable--changes in certain cases). To whatever extent the experimental data or the theoretical concepts are inaccurate, the model will also be inaccurate. The importance of such inaccuracies will depend on the magnitude of the errors in the region being examined by the model.

This qualification is important. If the data is good in, for example, the dose range of interest, it may not matter that it is poor for very much higher or lower doses. Conversely, if the data is poor in the dose range of interest, it may not help to have good data at very different doses.

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[a] Rasmussen, Norman C. Rasmussen on Reactor Safety, IEEE Spectrum, v. 12, Aug. 1975. p. 46-55.

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COMPREHENSIVENESS OF KNOWLEDGE

In a sense, comprehensiveness can really be considered an aspect of the status of technical knowledge. It specifically covers the situation where available information or knowledge is not complete. (The situation where complete information is available, but for some reason is not incorporated into the model, is explored as a matter of model complexity, below.) Comprehensiveness of knowledge is of real concern in a number of very complex cases scientists are attempting to examine.

For example, have environmental scientists identified all the complex competing and synergistic physical processes that occur in the atmosphere and effect such important factors as the atmosphere's ozone layer, and therefore radiation exposure from the sun; or carbon dioxide content, and consequently, possibly the long-term climate? Have scientists identified and incorporated all the mechanisms of chemical creation, destruction, introduction, and removal? Have they completely characterized all the interrelationships with altitude, with the population of each ion, atom or molecule in the atmosphere, with the incidence of collisions between elements, with the production of intermediate chemical agents, with transport processes due to circulation factors, with other atmospheric components such as dust, with diurnal considerations, with solar cycle considerations, with seasonal factors, with latitude factors, with the introduction of man-made agents such as airplane exhaust, industrial pollutants, etc., with cloud cover, with the earth's albedo, etc.? In a nuclear reactor, how do we know if scientists have identified every last possible event and sequence of events that can conceivably occur? Despite the many people who have contributed to such studies, is it possible that one of millions or billions of factors was left out, and that the omission is important in a certain very particular situation?

MODEL COMPLEXITY

For practical reasons, models very often simplify reality. This may be done because of computer time or cost, or because of research time and cost to create computer programs, collect data, perform tests, examine results, etc. There are real practical limits to what a computer can do. Even for simple operations, such as the division of two numbers, the division has to be truncated someplace, because some divisions would otherwise generate millions of digits and never end exactly. Enough digits are incorporated so that, in the case of a division process, the truncation is overwhelmingly of no real consequence, but that is a simple example of the fact that computer models must always cut off calculations somewhere, or limit the number of calculations that are performed, in order ever to end up with a result.

Normally, the mechanical simplications are of no consequence, and the methodological simplifications, such as decisions not to incorporate a certain level of detail–a minor physical process, for example–are made on the basis of good evidence that the effect is negligible, and therefore, are considered reliable. However, if major simplifications are made, such as in a quick preliminary study for exploratory purposes, or in a study that is done with insufficient personnel or time resources, or if simplifications are made where the evidence is not conclusive that the effect is minor in the region of interest, or if the data points are selected badly so they do not provide an accurate reflection of the trends operative, the reliability of the results can be affected.

CHAPTER 8: PROBABILISTIC ANALYSIS

INTRODUCTION

The term risk, as it is generally used in the study of individual and societal hazards, incorporates a measure of the magnitude or severity of the hazard and a measure of its probability of occurrence.[75] That is:

$$\text{Risk} = \text{Probability} \times \text{Magnitude}$$

Previous chapters have focused on methods of quantifying the magnitude and severity of the effect; this chapter examines methods of quantifying the probability, or chance, of occurrence.

Although this chapter will focus on the probabilistic nature of risks, it is important to understand that not all hazards are probabilistic. Consequences which occur with 100 percent certainty are known as deterministic consequences. In fact, either an exposure or an outcome can be either deterministic or probabilistic, depending on the certainty of the consequence in each case. Figure 7 illustrates how different consequences can be probabilistic, deterministic, or a combination of both, depending on the chances of exposure and of effect in given circumstances. Note that three of the four cases illustrated have at least one probabilistic element, and an analysis of these situations would involve some of the considerations raised in this chapter. In fact, the chance, or probability of a particular outcome often depends on a whole series of component factors, or events, each of which has some probability of occurrence. The net outcome of such a series of events is then a function of the probabilities of each of the component factors.

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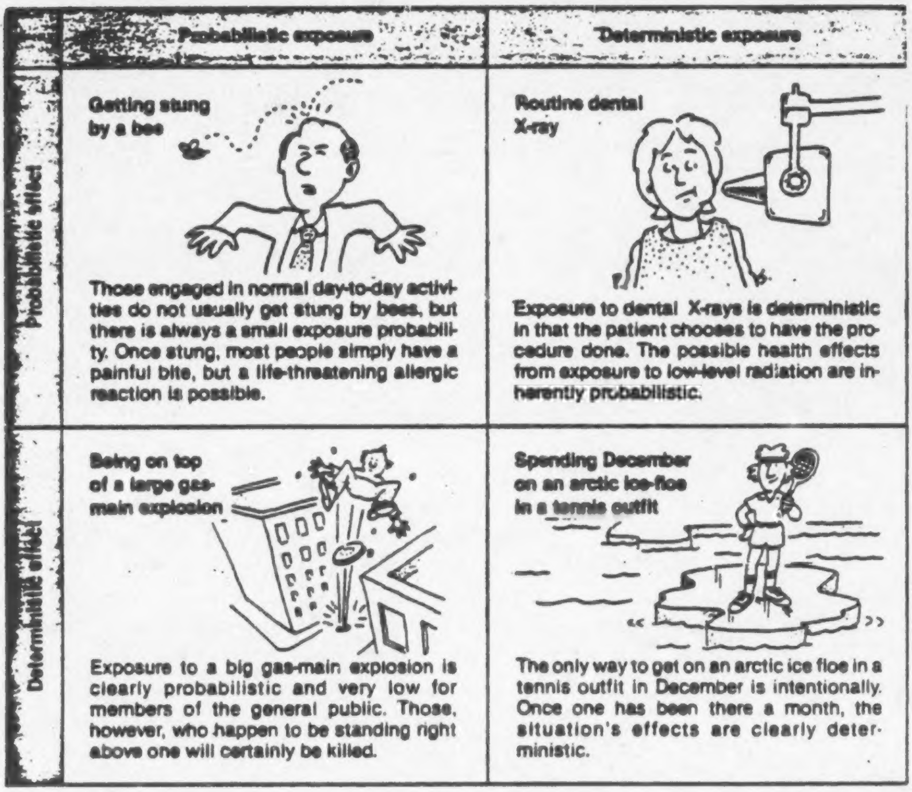
[75] Okrent, p. 1. Edmund Crouch and Richard Wilson. Risk/benefit analysis. Ballinger Publishing Co., Cambridge, MA, 1982. p. 9.

FIGURE 7.—PROBABILISTIC AND DETERMINISTIC EXPOSURES AND EFFECTS[a]


Probabilistic exposure
Deterministic exposure
Probabilistic effect
Deterministic effect
Getting stung by a bee
Routine dental X-ray
Being on top of a large gas-main explosion
Spending December on an arctic ice-floe in a tennis outfit

Those engaged in normal day-to-day activities do not usually get stung by bees, but there is always a small exposure probability. Once stung, most people simply have a painful bite, but a life-threatening allergic reaction is possible.

Exposure to dental X-rays is deterministic in that the patient chooses to have the procedure done. The possible health effects from exposure to low-level radiation are inherently probabilistic.

Exposure to a big gas-main explosion is clearly probabilistic and very low for members of the general public. Those, however, who happen to be standing right above one will certainly be killed.

The only way to get on an arctic ice floe in a tennis outfit in December is intentionally. Once one has been there a month, the situation's effects are clearly deterministic.

Given that a dose of a certain risk agent has a certain effect (dose-effect response) in human beings, these component factors can establish the exposure of the population to the agent for a particular set of circumstances, and therefore the net impact of a given incident. Depending on the risk agent, factors of interest might include:

The probability of a failure or a sequence of failures in an operating system that would result in a release of a certain quantity of risk agent;

The probability of weather patterns that would cause a certain dispersion pattern of the risk agent;

The availability and success of operation of institutional mechanisms such as evacuation procedures, or availability and use of protective equipment;

The biological concentration of the risk agent;

The probability of other natural events, such as earthquakes, that would influence the release of the risk agent;

The nature and extent of population exposure to the risk agent as a function of population distribution, demographics, mobility patterns, occupational patterns, daily or seasonal variations, etc.

Each of these, in turn, may depend on a series of subfactors with associated probabilities of occurrence. Many hundreds or even

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[a] Morgan, M. Granger. Probing the Question of Technology-Induced Risk, IEEE Spectrum, v. 18, Nov. 1981. p. 58-64. Copyright by IEEE, 1981.

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thousands of events may be involved, so the quantification of a risk effect through a risk assessment can become quite complicated.

This chapter focuses primarily on the important area of probability analysis of failures of complex man-made systems that might cause certain risks or lead to releases of risk agents, and also indicates how these analytical techniques fit with other analytical elements in determining overall probabilities of certain risk incidents.

METHODOLOGY OF PROBABILITY STUDIES[76]

Several methods are used to determine quantitatively the combined impact of the various factors which can influence the total risk. Major techniques which have been used in recent, and in some cases, extensive risk assessments to help define potential accident paths and their likelihood of occurrence are called event trees and fault trees. One of the early major studies made for a Government agency to develop and use these techniques for the quantification of technological health and safety risks to the public was the Reactor Safety Study of 1974, better known as the Rasmussen report.[77]

Fault trees and events trees are used to evaluate the projected reliability and failure rates of complex engineered systems whose failure rates are low enough so that they cannot be measured from operating experience in a reasonable amount of time. (They are also useful for improving reliability during the design stage before any operating history has been obtained.) Both these techniques are used to subdivide the possible causes of system failures into various subsystems or components whose failure rates can be estimated from previous experience with that type of subsystem or component. Basically, event trees define possible accident sequences and fault trees are used to calculate the probabilities of the events in these sequences. Figures 8 and 9 and the following discussion illustrate the differences between the two types of logic trees and how the component probabilities are related.

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[76] Based on Rasmussen on Reactor Safety, except where otherwise indicated.

[77] Reactor Safety Study: An Assessment of Accident Risks in U.S. Commercial Nuclear Power Plants—Summary Report, Aug. 1974, U.S. AEC, WASH-1400.

FIGURE 8.—SAMPLE EVENT TREE[a]

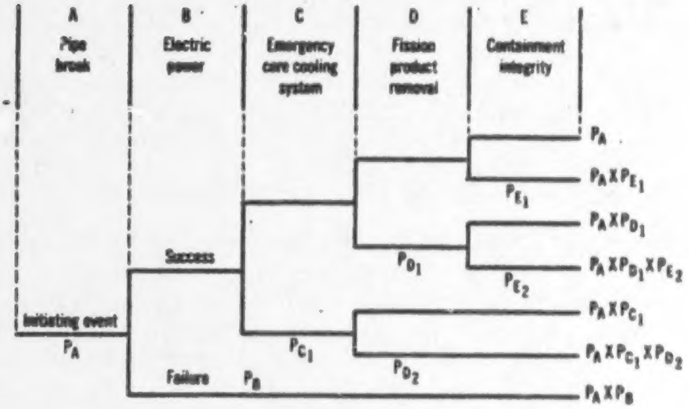
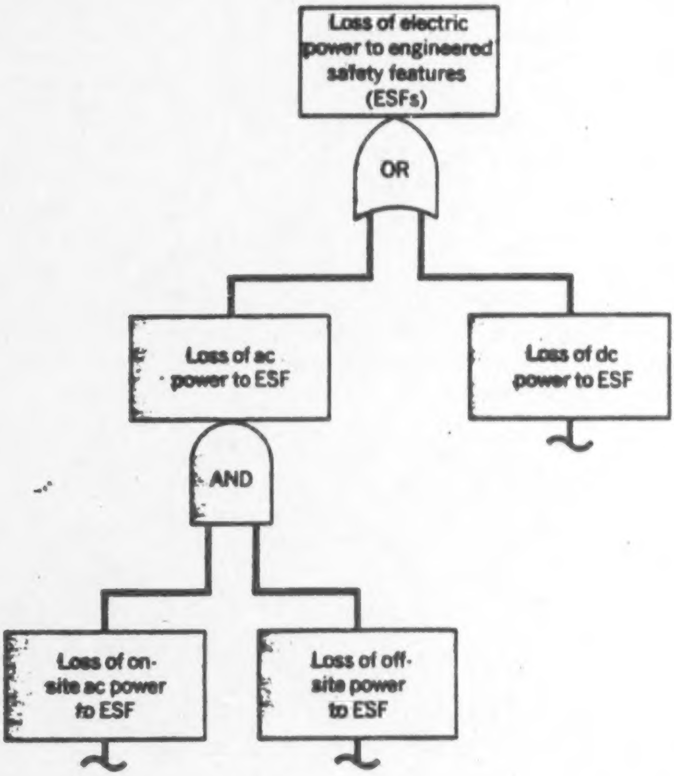

A
Pipe break
B
Electric power
C
Emergency core cooling system
D
Fission product removal
E
Containment integrity
Initiating event
P_A
Success
Failure
P_B
P_C1
P_D1
P_D2
P_E1
P_E2
P_A
P_A X P_E1
P_A X P_D1
P_A X P_D1 X P_E2
P_A X P_C1
P_A X P_C1 X P_D2
P_A X P_B

FIGURE 9.—SAMPLE FAULT TREE[b]—THE OVERALL PROBABILITY CORRESPONDS TO P_B IN FIGURE 8


Loss of electric power to engineered safety features (ESFs)
OR
Loss of ac power to ESF
Loss of dc power to ESF
AND
Loss of on-site ac power to ESF
Loss of off-site power to ESF

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[a] Rasmussen, Rasmussen on reactor safety. p.49.
[b] Ibid.

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In an "event tree," the basic objective is to identify the possible sequences of events following a particular initiating event.

> A event tree is an inductive logic diagram that consists of an initiating event and a series of branches leading through subsequent events to a defined end point, such as core damage. Each branch point represents a binary decision (failure or success with an associated probability for each) on the functioning of a given system that would be called upon as the event proceeded.[78]

Figure 8 shows a simplified event tree for a pipe break for a nuclear steam supply system. The different outcomes depend upon the operability of various systems after this initiating event. An actual event tree would generally be more complex and would include additional alternatives.

The "fault tree" employs a logic that is roughly the reverse of the event tree. It starts with some undesired event and traces back to the ways in which it may have occurred.

> A fault tree is a deductive analytical technique in which faults are postulated in binary fashion. Only faults that will contribute to a specific top event are considered. The tree is a series of logic gates showing a necessary relationship of events that will lead to successively higher events and eventually to a top event.[79]

Figure 9 shows a portion of a fault tree for loss of power to the emergency safety features of a nuclear reactor. Since either loss of ac or dc power to these features can cause the initial event, these two events are related to the outcome by an "or" gate.[80] In the next level, either off-site or on-site power is sufficient to maintain the AC power flow, so both must be lost to produce the loss-of-ac event. Therefore, they are related to the loss-of-ac event by an "and" gate. The remainder of the tree for the loss-of-dc event is not shown. The trees are traced back to events involving equipment for which failure rates are known from experience. It is then mathematically possible to calculate the probability of the final (top) event. In this case, this probability corresponds to P_B in the event tree (Figure 8).

The detailed study done of reactor safety provides a good illustration of how risk contributions from different probabilistic events can combine in a particular case. In the case of a nuclear reactor, the probability of a particular consequence that might affect people outside the plant depends first on the probabilities of internal systems failures discussed above, and then on how much of the radioactive material escapes from the containment, what the prevailing weather conditions are, and what population density exists in the contaminated area. The overall probability of a particular sequence of events is the product of the probabilities of these individual events. (Note: chapter 6 illustrates the multiplicative nature of probabilities.) Therefore, for the worst accident identified in the reactor safety study–the worst case result from an initiating event such as a small pipe break followed by failure of all emergency systems, under the worst case weather conditions (the wind blowing toward the highest population density):

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[78] Mallay, James F. NRC-Industry Cooperative Effort Sets Stage for Probabilistic Risk Assessment Studies, Nuclear News, v. 24, Sept. 1981, p. 87-92.

[79] Ibid.

[80] "Gate" is a term employed in logic to indicate a situation in which there is a branching of possibilities.

Probability of worst consequence = Probability of initial event X Probability of safety systems failures X Probability of containment failure X Probability of worst weather X Probability of population density.

Since the probabilities of each of the contributing events range from around 0.1 to 0.001, the overall probability of occurrence of the worst consequence in this particular case was calculated to be around 10^{-10} per plant per year.

PROBABILITY ESTIMATION

There are three major questions that can be raised about such a calculation of probability. They are: (1) Are the probability values used correct? (2) Are the probabilities independent (as implied by the multiplication)? (3) In obtaining the total probability, have all possible accidents been considered?

Correctness

The validity of the probability values used is based in large measure on knowledge of the probability of the initiating event. However, where very few such events have occurred, the statistical accuracy of actual data from operating experience to estimate the probabilities of many initiating events may be poor. In the case of pipe breaks in nuclear reactors, for example, the amount of uncertainty may be a factor of 10. Probabilities of failure obtained from fault tree analysis would be expected to have smaller uncertainties because these values are derived from events which occur more frequently, and therefore, are more accurately known.

In one study of 50 safety systems in the chemical, nuclear, and conventional power industries done by the Systems Reliability Service of the United Kingdom, observed failure rates were within a factor of 4 of the predicted values in 96 percent of all cases.[81] (Probabilities of failures of individual components may be much better understood and may therefore have even smaller uncertainties.)

Furthermore, it is customary engineering practice to attempt to use conservative values whenever there are uncertainties in an analysis. Therefore, the probability estimates are generally likely to represent upper bounds on the probability of failure. In fact, in the British study, the observed failure rate was, on the average, about 25 percent smaller than the predicted rate.[82] The practice of placing an upper bound on a probability of occurrence based on the years of operating experience in which no accident has occurred is one such conservative estimating technique. When the experience is very limited, this practice may overestimate the probability of occurrence of an event, and increase the level of public concern about the perceived impact of a hazard.

Independence

A simple multiplication of probabilities assumes that the probabilities are independent; that is, that one failure does not precipitate another. However, there are cases in complex systems where one failure can directly cause another. These interdependent failures are known as "common mode" failures. Although, of course, major systems are designed to prevent most of these so-called common mode failures, because of the sheer complexity of many major engineering systems and the number of interactions possible, it would be virtually impossible to eliminate totally all conceivable sources of common mode failures. Such dependencies must therefore be considered in a probabilistic analysis in order to adjust probability factors appropriately. Any existing common mode failure sequences not identified in the analysis would tend to increase the calculated probabilities since they would basically remove one or more fractions from the sequence of multiplications.

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[81] Rasmussen, p. 49.
[82] Ibid.

Completeness

Any analysis can consider only those accidents that can be imagined by the individual and collective imaginations of those conducting the analysis. Since presumably not all possible failures–in hardware, in maintenance, and in human interaction–have yet been observed for many of the systems of concern, there could quite possibly be accidents that have not yet been identified. This possibility has been a major source of criticism of probabilistic risk assessments. As additional experience is accumulated, data bases, of course, can be modified and refined. However, there has been considerable experience with the major components of most systems of concern (i.e., pipes, pumps, valves, switches, and the like); thus, it is considered unlikely that the most probable and, therefore the most dominant, modes of failure have been overlooked. The very rare or unusual failure modes that may not have been recognized would be expected to change the overall failure probabilities very little, although the consequences of the accident such modes could cause could vary from negligible to very large.

CHAPTER 9: COMPARATIVE ANALYTICAL TECHNIQUES

INTRODUCTION

Since almost all human activities embody some risk, it is often not sufficient to know only that there is a certain degree of risk associated with a particular activity. It may be more useful, in many cases, to evaluate a given risk in some comparative framework. There are several possible frameworks for comparison: the risks of alternative methods of accomplishing the same objective can be compared, or the risks of a given action can be compared with its benefits in any of several ways. All these techniques draw upon risk estimates made on the basis of the analytical techniques discussed in previous chapters.

Comparative analytical risk assessment techniques are particularly useful in the context of regulatory activities.[83] While it is not the purpose of this document to discuss regulatory alternatives per se, the important regulatory applications of the various analytical techniques will be noted. The use of analytical techniques in regulatory decisionmaking is also the subject of some moral and ethical concerns which will be outlined briefly.

ANALYTICAL TECHNIQUES [84]

The terminology in the emerging field of comparative risk analysis can be somewhat confusing. This section discusses the major methods of risk comparison, as they generally seem to be defined. The terminology in current use, and the methodologies generally associated with each of these follows.

Cost-benefit or *benefit-cost* analysis, which in the context of reducing risk defines a benefit as a reduction in damages, and provides for a comparison of the monetary value of a given benefit with the cost required to attain it. Pure cost-benefit analysis assumes that all benefits and costs can be translated into monetary terms.

Cost-effectiveness analysis, often considered a special case of cost-benefit analysis, can be used when the benefits are considered to be difficult to express in monetary terms. In principle, the cost-effectiveness framework is used to establish the costs of achieving different levels of benefit, thereby providing a quantitative method for selecting a solution which optimizes the benefit for a given expenditure of funds or minimizes the total cost.

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[83] The importance of comparative methods is highlighted by congressional hearings held on the subject. U.S. Congress. House. Committee on Science and Technology. Subcommittee on Science, Research, and Technology. 96th Congress, 2d Sess. Hearings on Comparative Risk Assessment. May 14-15, 1980. 571 p.

[84] Except as noted, this section is based on Benefit-Cost Analysis In Air Quality Management, G.L. Brady and B.T. Bower, ES=T, v. 15, Mar. 1981, p. 256-261.

Risk-benefit or *benefit-risk* analysis, is also closely related to cost-benefit analysis. In risk-benefit analysis, generally only the benefits are quantified in monetary terms, whereas in pure cost-benefit analysis, both quantities are generally quantified in monetary terms. The choice of method usually depends on the availability and acceptability of monetary equivalents for all risks and benefits involved. Brady and Bower draw the distinction of using cost-benefit analysis to measure the impact of a regulatory action in reducing risk, and risk-benefit analysis to measure the impact of removing or reducing a regulatory action and thereby increasing risk. From a strictly mathematical point of view, of course, both methods are equivalent, but such a risk-benefit analysis views the costs saved by the reduction in regulation as the benefit, to be measured against the increased health and safety risk, while such a cost-benefit analysis views the reduction of the risk as the benefit, to be measured against the cost of achieving it.

Risk-risk analysis is an important alternative methodology, since it avoids the necessity of comparing or contrasting a cost, or a risk, incurred versus a benefit achieved, and focuses instead on the comparative risks of alternative ways of solving a problem. A primary application of this method is in comparing two or more different ways of achieving exactly the same end–such as supplying a given amount of electrical power using alternative energy resources (coal versus nuclear, for example). The method can also be used to compare the risks of doing something to the risks of not doing it, when both alternatives carry some degree of risk. This is applicable to such decision processes as those involving the use of nitrates in processed meats, where the risks of nitrate induced cancers must be balanced against the risks of botulism from nitrate-free processed meats. One difficulty with risk-risk analysis is that the types of risks associated with alternative solutions may not be similar enough to be directly comparable, thus leading to some of the same necessity for quantifying risk that occurs in the case of other risk-comparison methodologies as well, and which will be discussed in greater detail below.

ISSUES OF RISK COMPARISON [85]

All of the risk comparison techniques outlined above are subject to uncertainties in the analytical results based on errors or uncertainties in the estimates of the quantities used as inputs in the derivation of the results. The numerous possible difficulties in deriving estimates of risk using various analytical techniques have already been discussed in the previous chapters. Cost estimates for the development, procurement, and operation of advanced technological systems, such as might be employed to produce an overall reduction in levels of risk associated with some important activity (for example, the addition of scrubbers to a coal-fired power plant) can also be subject to a great deal of uncertainty, and the history of cost-estimation includes many examples of large errors in estimates.[86] This is particularly true for systems which are in the early stages of development, where little practical experience exists on which to base predictions of performance and costs. The problems of cost estimations for engineering development, construction and operations is a separate subject in itself and is beyond the scope of this study, but suffice it to say that all such estimates are subject to a great deal of uncertainty until a reasonable amount of operating experience has been achieved.

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[85] For further discussion of, and a variety of perspectives on, the issues of cost-benefit analysis and other comparative techniques see, for example: U.S. Congress. Senate. Committee on Science and Technology and Committee on Commerce, Science, and Transportation. Risk/Benefit Analysis in the Legislative Process. Joint Comm. Print. 96th Cong., 2d Sess., U.S. Govt. Print. Off., 1980. Steven Kelman. Cost-Benefit Analysis–An Ethical Critique, Regulation, v. 5, Jan./ Feb. 1981, p. 33-40. The Limits of Cost-Benefit Analysis, Report from Center for Philosophy and Public Policy, v. 6, Summer 1981, p. 9-11. Sheldon W. Samuels, Role of Scientific Data in Health Decisions, Environmental Health Perspective, v. 32, 1979, p. 301-307. Michael S. Baram, Cost-Benefit Analysis: An Inadequate Basis for Health, Safety, and Environmental Regulatory Decisionmaking, Ecology Law Quarterly, v. 8, 1980, p. 473-531. Kenneth T. Bogen, Public Policy and Technological Risk, Idea, v. 21, p. 37-74. David Okrent, Comment on Societal Risk, Science, v. 208, Apr. 25, 1980, p. 372-375. Chauncey Starr and Chris Whipple, Risk of Risk Decisions, Science, v. 208, June 6, 1980, p. 1114-1119. Paul Johnson, The Perils of Risk Avoidance, Regulation, May/ June 1980, p. 15-19. S.C. Black and F. Niehaus, How Safe is "Too" Safe?, IAEA Bulletin, v. 22, Feb. 1980, p. 40-50.

Another factor of concern is that of making appropriate comparisons. This concern exists in many risk analyses, but can be most readily illustrated by looking at a complex comparison, such as that of risk from alternative energy sources. In comparing risks of different energy producing systems, for example, major questions which need to be addressed include: What steps of the energy production cycle should be included? If one looks just at the power production step, solar energy may appear much safer than other technologies, but if other steps are included, mining or manufacturing accidents may alter the relative risks of different technologies. Furthermore, different assumptions about technologies used (such as open pit versus underground mining) will also affects the risk results. How should risks be allocated between energy and non energy sectors? Should all alternatives be sited identically or should each be optimized? Should equal energy production capacities for each energy source be assumed, should the energy supply mix be assumed to remain constant, or should some other allocation between energy sources be assumed? Where only pilot energy plants have been operated, what kind of performance should be assumed for a full-scale plant? Pilot plant performance may be a poor indicator of performance potential, but other assumptions would be hypothetical. What assumptions should be made for power plant replacements? If no replacements are assumed, advanced technologies for the newer energy sources may appear relatively better than if existing outdated power plants for more established energy sources are assumed to be replaced by advanced versions of the same technologies. How should possible long-term consequences be counted? How should low-probability high impact events be counted? These and other such questions are one important element of the controversy surrounding different studies of comparative risks of different energy sources.[87] Failure to properly—or at least consistently—account for such factors leads to impacts on risk assessments ranging from the very subtle to the patently absurd; e.g., as statements that electric automobiles don't pollute, as opposed to the reality that they don't produce air pollution where they are driven, but do produce pollution at the sites of the power plants from which they derive their electricity.

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[86] Costle, Douglas. The Decisionmaker's Dilemma, Technology Review, v. 83, July 1981, p. 10-11.

[87] For reviews of some recent energy studies, see for example: A.V. Cohen and D.K. Pritchard, Comparative Risks of Electricity Production Systems: A Critical Survey of the Literature, Health and Safety Executive, Research Paper 11, London 1980. See also U.S. Congress, 97th Congress, 1st Sess. House. Committee on Science,and Technology. Hearings on Societal Risks of Energy Systems, June 18, 1981. 155 p.

Of particular interest, for purposes of this study, is the difficulty of incorporating risk estimates into a framework suitable for analytical comparisons useful for decisionmaking. In the first place, risks come in many forms, and many risks cannot even be compared directly to each other. Health and safety risks can occur in the form of mild or serious injuries, temporary or chronic illnesses, immediate or delayed death. Other risks that may be important in particular cases may not be directly related to human beings at all, but rather to the environment, to the ecology, to future generations, or even to our economic welfare or national security.

Many of these risks can be translated into a common metric in order to be able to compare them and to make decisions among different alternatives based on the degree of risk associated with each, but the translation of these risks into common terms involves deliberate analytical decisions that should be understood in order to make appropriate use of the resulting risk values. Furthermore, the use of such common metrics is subject to disagreement on some very fundamental grounds that form a large part of the background for the controversy over the use of risk assessment in regulatory decisionmaking.

Looking primarily at health and safety risks, it is clear that there are a number of ways that dissimilar risks can conceptually be compared. Some of the common metrics for such comparisons have included: work-days (or personal income, or tax revenues) lost due to injury, illness, or death; costs of medical treatment of illness; decrease in expected life-span, particularly where long-term illness leading to death is involved; insurance payments associated with the injuries, illnesses or death, as a measure of the cost to society; the costs of training a person to replace a worker lost from the work-force due to long-term injury, illness, or death; etc.

The examination of these metrics for the comparison of risks raises several important questions: when is it appropriate to use one or another or these metrics; what conclusion can be drawn in cases where the different methods provide very different results; how is pain and suffering, both to the individual and to his/her family, incorporated into these equations; do some of these measures inherently put a different value on different people, such as where the costs of education and training are used, or where the work-days lost are translated into a dollar value?

Clearly, most of the measures listed above are either already expressed in monetary terms, or are directly and readily translatable into such terms. And perhaps the greatest concern regarding the use of comparative analytical techniques in risk assessments relates to disputes over the presumption that all human damages can be quantified in monetary terms. The debate has strong moral and ethical overtones, particularly where estimates of the value of a human life are involved. It is beyond the objectives of this paper on risk assessment techniques to provide a detailed examination of the debate surrounding risk assessment applications. However, many of the questions stated above are basic to the concerns raised in this regard–that is, should we factor in pain and suffering, and if so, how; and should or should we not make assumptions that effectively assign different values to the lives or health of different people, or different values to lives lost because of different risk agents (depending on the economics of the associated industry)?

Some critics of the use of analytical methodologies, in fact, question the basic presumption that different kinds of risks can be compared in a common scientific metric at all. Opinions, of course, cover the spectrum of viewpoints, but some of the major concerns of the critics are indicated below. Critics of risk assessment argue that assigning numerical values to risks and benefits is quantifying the unquantifiable. This, they feel, lends a false air of scientific legitimacy to the results, and they are too likely to be regarded as the "right answers" when compared to judgmental, qualitative viewpoints. They also raise concerns about the possible development of an aristocracy of the technical elite. The scientists and engineers responsible for risk assessments could, in their view, exert considerable influence over societal decisions if the results of their analyses become a primary basis for decisionmaking. They raise questions about the motivations and ethics of such a technical elite, and about their accountability to society. They argue, therefore, that it is preferable that decisions be based on democratic processes rather than on purely scientific ones. Critics of risk assessments further question whether society should deliberately make any decisions based on utilitarian economic considerations or risk tradeoffs if such a decision is expected to involve any risk to human life. This would imply that they would not want to knowingly make a decision that will result in the sacrifice of even one life, for any reason, even to reduce another risk. They assert that cost effectiveness is not a sufficient decision parameter; if human lives are involved, it is worth any cost to save even one life.

Proponents of the use of risk comparisons make the observation that even no decision is a decision of sorts. All energy sources are believed to carry some degree of risk. Should we shut down everything and risk death from exposure rather than from pollution? Should we build safer power plants, even if they are so expensive to operate that utility customers will have to choose between food and heat? Should we keep the plants we have in operation, but not build any more or replace any old ones? If we build more, how should we make the decisions as to what type to build and where to put them without some kind of comparative technique? If we allow each individual to supply his/her own energy needs, and thus avoid the undesirable situation of having society per se impose a decision that creates risk for certain individuals, what do we do if an individual uses a system that imposes risks on other individuals? While it is perhaps not satisfying to assign a dollar value to human life, they argue, it at least provides some way to sort through a very complex set of parameters and to make decisions that minimize the overall risk. They assert that, without such analysis, the diversion of funds to reduce one risk could result in increased risks from other sources, or that beneficial and necessary technologies will be priced out of commercial feasibility.

The Nuclear Regulatory Commission, in a decision on a petition to shut down the nation's nuclear facilities, noted that:

> It appears likely that many government actions affecting a complex society with a population of over two hundred million could be connected by a plausible chain of causality to at least a small number of premature deaths. Presumably, under the petition's interpretation of the Fifth Amendment, all these activities would have to cease. Logically, however, the cessation would be equally unconstitutional because the licensed activities—ambulances or power plants—also save lives.[88]

This debate has not been resolved. Many of these comparative analytical techniques are nevertheless being used to varying degrees in different situations. The nature of the debate over their use is perhaps partly responsible for the fact that they are used differently in different situations. Therefore, it is important to understand the capabilities and limitations of these techniques, as well as to understand the complexity of the environment in which they are being used.

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[88] As reported in NRC Rejects Petition for Nuclear Shutdown, INFO 157, Aug.-Sept. 1981, p. 5.

CHAPTER 10: BRIEF SYNOPSIS OF RISK MANAGEMENT A*ERR20*PPROACHES

INTRODUCTION

Although this study deals primarily with issues relating to risk assessment, it is helpful to have a basic understanding of the possible ways in which risks can be dealt with, or managed, in the public and private sector. The importance of risk management to a risk assessment study lies in the fact that most of the efforts to manage risk rely on one or more of the scientific and mathematical processes of risk assessment discussed in this report. This chapter identifies and outlines briefly the major approaches to risk management and notes the roles of risk assessment in each.[89]

MAJOR APPROACHES

One way of categorizing risk management approaches is by the major philosophical imperatives that motivate them. Major risk management approaches that can be identified in such a fashion are: risk-only (or no-risk); technologically-determined risk (i.e., best available technology); risk balancing, using either costs (as low as reasonably achievable) or comparative consequences (risk-risk); and free market decisionmaking. This breakdown, although not the only way to categorize risk management approaches, provides a convenient framework for a discussion of the different roles risk assessment can play in efforts to control technological risks, and the different scientific data bases that may be required, and is so utilized in the discussion below. Table 10 shows some major examples of risk-related legislation that have been enacted in the above categories of risk management, and also lists the responsible Federal regulatory agency.

The selection of a particular risk management approach depends on many factors, including public attitudes and perceptions about risk agents in general and about any particular risk agent, the nature and potential severity of the risk, and possible institutional arrangements for managing that risk. The role of public perception and issues relating to types of impacts have been discussed elsewhere in the report. The question of possible variations of institutional arrangements for managing and regulating risk is a complex subject in itself and will not be examined in this report; however, the major alternatives--not necessarily mutually exclusive--include direct legislation, regulatory agencies, judicial approaches, and reliance on the marketplace. A variety of recent publications discuss the pros and cons of alternative approaches for risk management

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[89] For a more detailed discussion of risk management options, see for example, Lubin, Barry and Thomas Moss. Risk Analysis: A Legislative Perspective. Environmental Toxicology and Chemistry, v. 1, p. 1-13, 1982.

TABLE 10. EXAMPLES OF STATUTORY RISK MANAGEMENT APPROACHES [a]

Statutory approach	Agency
Technology-Only:	
Clean Air Act (certain provisions)	EPA.
Federal Water Pollution Control Act (certain provisions)	EPA.
Risk-Only:	
Solid Waste Disposal Act	EPA.
Federal Food, Drug, and Cosmetic Act (Delaney clause, 21 U.S.C. 348(c)(3)(A)	FDA.
Federal Aviation Act	FAA/DOT.
Balancing:	
Federal Insecticide, Fungicide, and Rodenticide Act	EPA.
Toxic Substances Control Act	EPA.
Federal Meat Inspection Act	USDA.
Consumer Product Safety Act	CPSC.
Atomic Energy Act	NRC.

[a] Bogen, p. 6.

in greater depth.[90] Different types of institutional arrangements may also have different implications for the role of risk assessment, particularly regarding the determination of who performs a risk assessment and who utilizes it. Such considerations are touched upon briefly in the discussion below.

No-Risk

No-risk (or "risk-only") regulations require that no risk agent subject to this risk management method be put into general use if any level of risk has been identified. The Delaney clause, 21 U.S.C. 348(c)(3)(A), is the major example of this approach. This clause prohibits the use in foods of any substances which have been found to cause any type of cancer at any level in any animal experiment. In a sense, this is probably one of the simplest regulatory methods. It requires only data from scientific experiments, and avoids some of the technical and ethical problems attendent in using other elements of risk assessment (discussed in this report). It can be legislated directly, and thus the responsible regulatory agency need assume only an enforcement role, not a risk-setting one. This risk management approach is intended to provide maximum protection to the public from the risks of a given substance.

However, this approach does not credit a substance for any risks it might prevent. It also does not provide for regulatory decisions to incorporate economic concerns, the availability of substitutes, the public acceptability, or other factors. Some of the difficulties of a no-risk approach are illustrated by the controversy over the issue of the use of saccharin. In this case, the Delaney clause mandated that saccharin be removed from the marketplace when research revealed a risk of bladder cancer in animals, but the substance in question was already in widespread use, had a high degree of public acceptance, and was considered to have definite benefits to certain elements of the public (diabetics and some overweight individuals).[91] The resolution of this case is still at issue.

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[90] See, for example; John Mendeloff, Reducing Occupational Health Risks: Uncertain Effects and Unstated Benefits, Technology Review, v. 82, May 1980, p. 66-78. Robert A. Squire, Ranking Animal Carcinogens: A Proposed Regulatory Approach, Science, v. 214, Nov. 20, 1981, p. 877-880. John H. Weisburger and Gary M. Williams, Carcinogen Testing: Current Problems and New Approaches, Science, v. 214, Oct. 23, 1981, p. 401-407. Proposed Systems for Food Safety Assessment, Food Safety Council, June 1980. Kenneth T. Bogen, Coordination of Regulatory Risk Analysis: Current Framework and Legislative Proposals, CRS 81-209 SPR, June 19, 1981. Science, Technology, and the Limits of Judicial Competence, Shelia Jasanoff and Dorothy Nelkin, Science, v. 214, Dec. 11, 1981. David Bacelon, The Judiciary: What Role in Health Improvement? Science, v. 211, Feb. 20, 1981, p. 792-3. Harold Markey, Risk Assessment and the Law, C and EN, Nov. 24, 1980.

Best Available Technology (BAT)

The best available technology approach is a "technology-only" approach to risk management. That is, decisions are determined only by the technology. This approach mandates the use of the best available version of a technology (such as different emission control systems) to reduce a risk, regardless of cost. This requires a knowledge of the levels of risk possible with different technology, and therefore generally involves the use of risk assessment techniques which examine mechanisms for the release and dispersion of risk agents with different technological options. This type of approach has been used in some environmental regulation.

This BAT approach is not applicable to all sources of risk; it applies primarily to risks which can be reduced by electro mechanical systems. Therefore, it is employed primarily by agencies having responsibilities involving complex technological systems, such as the Environmental Protection Agency has for power plants and industrial process plants. This approach also does not specifically identify an end-point to the application of best available technology, i.e., how much redundancy should there be in safety systems? The major concern about this approach, however, is economic; once again, this mechanism does not take into account any economic or other considerations that may be important. Another concern is that it effectively specifies the technology at the time of regulation that should be used in a given case, which brings with it the potential hazard of stifling innovation.

As Low As Reasonably Achievable (ALARA)

The ALARA approach to risk management is based on evaluations of the cost-effectiveness of different alternatives for reducing risk. Thus, it incorporates some of the economic considerations lacking in previously mentioned approaches. However, as has been discussed, there is considerable uncertainty in some of the values that may be incorporated in a cost-effectiveness analysis, and there is some controversy over whether such purely analytical techniques are useful where human life may be at stake. A basic problem with this approach is that there is no objective, consistent level of "reasonableness." Reasonableness implies some sort of balance between levels of risk and economics, but there is no simple, universally agreed upon point at which that balance can be said to exist.

Risk-Risk Minimization

The risk-risk minimization approach to risk management compares the risks of different technological alternatives for accomplishing a given objective in order to determine the alternative with the lowest risk. It therefore looks at a given situation from a broader perspective than does a simple comparison of the risks of a single technological option with different risk-abatement measures applied to it. For example, rather than simply examining the reduction of pollution risks from coal burning possible by using various emission control systems, a risk-risk minimization might also compare the reduction of pollutant levels and associated risks possible from burning coal that has been chemically and mechanically processed to remove sulfur compounds; from synthetic liquid fuels produced from coal; from using fuels other than coal; or from other technological options.

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[91] Sarah Fritschner. A Question of Risk. Washington Post, Oct. 15, 1981.

Risk-risk minimization is, in a sense, a variant of the ALARA approach, in that it is used to select the most "reasonable" alternative; in this case, however, that selection is from among several different technologies rather than simply from among ways to "fix" a single technology. Consequently, a risk-risk comparison uses risk assessment results in substantially the same way as does the ALARA approach, but generally requires information on a larger and more diverse range of options. One difficulty in applying this approach is that the different technological options considered may differ in many ways other than risk and cost–such as technological state-of-the-art, resource availability, convenience, reliability, national security implications, attractiveness to the public, etc.–so a comparison of options becomes considerably more complex.

Market Regulation

The free market approach to risk management maximizes the economic element. With this approach, Government is not directly obligated to set specific limits for individual cases or to specify the method of reducing risk, but rather allows the marketplace to make these decisions. In one variant of a marketplace approach, regulatory limits for such risks as environmental pollutants can be applied at a regional level, allowing affected industries to allocate these limits according to market mechanisms, so that economics determines whether pollution abatement technologies are used or whether some other operational solution is applied. This, of course, is also regulation, but at far lower a level than in the case of specifying limits for each individual industry.

The Reagan Administration has taken the position that the number and complexity of Federal regulations, including risk-related regulations, has been hampering the free and effective operation of the marketplace, and therefore, is at least partly responsible for our current economic situation. President Reagan favors an approach that minimizes the number of regulations and the extent of regulatory intrusion into the activities of the private sector, and therefore maximizes the freedom of activity in the marketplace. Under the free market approach, regulatory agencies' responsibilities will be reduced and/or changed, and different uses may be made of risk assessments. The responsibility for supporting and utilizing risk assessments will fall much more heavily to the private sector, and methods of risk evaluation that incorporate economic arguments will be of major importance.

The free market approach depends critically on the consumers having and understanding the often complex information that would allow them to make economic decisions that incorporate risk information. Therefore, one concern with this approach relates to the difficulty of packaging and disseminating the technical information required for decisionmaking in a fashion that will make it broadly available and understandable, but not oversimplified. Another concern is that, even given all appropriate information, individual decisions may or may not reflect concern for other members of society, now or in the future, or for the environment.

Even an environment that permits more of a free market approach is still likely to operate under a variety of legal and statutory authorities. Such authorities might include regulations of regional pollution levels, discussed above, or legislation establishing legal liability for the effects of discharged wastes or other risks. These might have important effects on the way in which the free market effectively does operate. Nevertheless, a reduction in regulation is likely to lead to a mode of operation closer to that of a classic free market than is presently the case.

CHAPTER 11: CONCLUSION: ROLES OF RISK ASSESSMENTS

INTRODUCTION

Risk assessment is effectively a new tool developed by the scientific community to help better understand and manage the risks to public health and safety and to the environment caused by some applications of science and technology. While it offers new insights and ways to think about risks, it also has a number of inherent limitations that have been addressed in this report. These limitations, and the concerns they engender, must be considered in developing and implementing Government programs for managing risks. Therefore, Congress in its deliberations on Federal risk management approaches will need to understand the potential uses and limitations of risk assessments and how these considerations affect specific risk management legislation.

The foregoing chapters have discussed the salient characteristics of risk assessments and the primary issues which presently surround them. Major themes which emerged from the discussion include: the uncertainties of risk analysis and the impacts of these on the use of risk assessments; the ethical considerations involved in managing risks and the consequences of these on the uses of risk assessments; and the present multiplicity of roles for risk assessment under different risk management philosophies and different institutional management arrangements. This summary highlights some of the major points addressed in the report and suggests how these may impact the roles risk assessments can play in the management of technological risks. Some of these issues will be of particular interest to the Congress over the next few years as it deals with a variety of legislation concerning risk, risk assessment, and risk management.

UNCERTAINTIES

Perhaps the major message that recurs throughout this report is the fact that risk assessments necessarily are subject to a host of uncertainties and errors–in the epidemiological data, the biological data, the models used, etc. In many cases, errors from such effects are minor, but that is not always the case. If the recognition of the risk is new, or if the typical exposures are at doses for which the effects are difficult to measure and quantify, the resulting risk assessments may be subject to larger uncertainties.

Does this mean that risk assessments cannot be used? Generally they can be, but with great caution and attention to uncertainties. In the first place, it is essential to examine any particular risk assessment in the areas outlined in this report to determine what weaknesses, if any, it may suffer. If there is recognition of the range of uncertainty of the results of any particular analysis, it may be possible to incorporate appropriate adjustments into the management schemes chosen. For example, a comparison of alternative risks may use "worse-case" comparisons rather than the mid-range figures to be certain any error is on the side of conservatism. Thresholds for exposure may be set incorporating a margin of safety over the nominally safe value.

Secondly, risk assessment results may be reinforced or corraborated by findings from other research involving the same risk agent, with the uncertainties thereby reduced. Thus, data that is generally not utilized independently, such as cellular research results, may provide supporting evidence to data from epidemiological studies or experiments with animals. Some recent studies on the applications of risk assessments suggest specific formulaic procedures for aggregating the evidence of different studies, including ways of sorting between conflicting findings.[92]

Finally, an understanding of the shortcomings of particular risk assessments and the capabilities and limitations of different assessment methodologies can lead to the identification of appropriate and potentially fruitful paths for further research to reduce the uncertainties in the risk assessments. Conversely, better understanding can help to avoid expenditures of funds and efforts in directions less likely to improve the analysis, for example, data collection in a dose range which will not yield statistically valid results, or which cannot reliably be correlated with doses of interest.

ETHICAL CONSIDERATIONS

Another major factor discussed in this report is that of ethical considerations relating to risk assessments. Ethical concerns relating to specific elements of risk analysis have been discussed in chapter 9 and will not be repeated here. One broad factor that merits special mention is the impact certain ethical considerations may have on the question of whether risk assessments should be used at all.

One element of such concern is the ethical dilemma involved in knowingly exposing, or permitting the exposure of, some element of the population to a risk. Key questions are: Does it matter who the exposed people are? Whether they know about it? Whether there is some counteracting benefit to human life or health? If decisionmaking based wholly on ethical considerations prevails–i.e., that government bodies should not deliberately establish or permit a risk to individuals–very little risk assessment would be needed, except perhaps that useful for individual decisions. Virtually everything with known risks presumably would be banned. However, current trends, economic considerations and other factors seem to portend an approach based on a more complex set of considerations.

A related argument seems to be that public acceptability criteria, rather than pure scientific considerations or pure ethical considerations, should prevail. The argument here is that ultimately the public should get what it wants, that experts may advise but should not decide. Since public acceptance of certain risks is not always closely correlated with the findings of risk assessments, and the role of risk assessment research in molding public opinion is not always clear, this would seem to indicate a lower priority for risk assessment research. On the other hand, there is an opposing moral question regarding how much weight a government agency can ethically give to public acceptability in making risk management decisions if the available evidence indicates that following the public perception would produce a greater risk to the public than some other possible alternative.

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[92] See for example: Proposed System for Food Safety Assessment, Food Safety Council, June 1980.

Another apparent element of some ethical arguments relates to the present uncertainties in risk assessments, discussed above. If we really had good data on the risk agents and their effects, the reasoning goes, we could use risk assessments, but lacking adequate or reliable data, the use of risk assessments alone might lead to erroneous decisions. Therefore, it is better to avoid the use of risk assessments in decisionmaking. On the other hand, others claim that risk decisions must be made on the basis of uncertain assessments, because waiting for perfect information without interim action may incur a greater risk.[93] A regulatory approach that can adapt with changes in knowledge might satisfy some of the ethical concerns over the uncertainties.

MANAGEMENT APPROACHES

One thing that is apparent from the very brief review of risk management approaches in the previous chapter is the great variation in analytical and regulatory approaches, and in management authorities, that can be, and are being, used for different risk agents, and the consequences these differences have on the need for risk assessments. At present, these differences imply that risk assessment efforts should be tailored according to the use that can be made of them under current legislation and regulatory practice.

However, over the longer term, the diversity of current risk management practices raises the question as to whether there should be a greater consistency in how risks are managed. Some particular questions of consistency that relate to risk assessment are: Is appropriate and consistent use being made of available scientific data in all risk areas? Who is responsible for review of the quality of risk assessments? Do the circumstances of different risks, as revealed by risk assessment techniques, warrant the different risk management approaches being employed? To what extent does the diversity of risk managers fragment and weaken the development of risk assessment? Does fragmentation prevent a critical mass of funding in any single risk area, or adversely inhibit the interchange of research information between researchers in different risk fields? Alternatively, does diversity strengthen risk assessment by providing more contributors and perspectives to it?

Finally, the diversity of risk management approaches currently in use is sometimes regarded as providing an experimental "proving ground" for risk management. If this is so, can risk assessments be used to improve the experiment by providing objective criteria for the selection of management approaches in particular cases? How should risk assessments be structured to ensure that necessary information will be available if the "failure" of an experiment prompts a change in the direction of risk management, either in general or for particular risks? Should we develop some criteria for risk *management* assessment?

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[93] Jellinek, Steven D. On the Inevitability of Being Wrong, Technology Review, v. 82, Aug./Sept. 1980, p. 8-9.

Thus, there are a number of important questions and issues regarding risk assessment and its role in the public management of risks. These questions and issues may well grow in importance in the coming years as our technologies grow increasingly complex and pervasive, as the increasing sophistication of scientific research provides more and more information on risks, and as the American public grows increasingly aware of risks, ways of countering them, and controversies surrounding them. If so, questions of the role of risk assessment, and concerns about its validity, its value, and its appropriateness can also be expected to grow in importance. Consequently, the role of risk assessment will probably remain a subject of considerable congressional attention and importance in the coming years.

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